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**Investigating the Relationship Between
Physical Activity and Myalgic
Encephalomyelitis/ Chronic Fatigue Syndrome**

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Investigating the Relationship Between Physical Activity and Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

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Declaration

I declare that this thesis is entirely my own work and represents the results of my own research carried out at Teesside University. I declare no material within this thesis has been used in any other submission for an academic award.

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating illness characterised by severe fatigue which causes a significant reduction in levels of activity. Post exertional malaise (PEM), unrefreshing sleep, cognitive impairment, and/ or orthostatic intolerance are all key symptoms of the illness. PEM is described as a unique attribute of ME/CFS which results in significant worsening of symptoms following a physiological, cognitive, or emotional stressor. Due to this, those with ME/CFS are required to manage their activity levels to control PEM symptoms. Nevertheless, there is some evidence that graded exercise interventions could improve symptoms in ME/CFS although this is contested with some arguing that graded exercise programmes cause a worsening of symptoms. The aim of this thesis is to explore the relationship between ME/CFS and physical activity.

Methods and Findings: The first objective was to assess if people with ME/CFS had a reduced peak oxygen uptake (VO_{2peak}) compared to apparently healthy controls as this may increase their risk of all-cause mortality. A meta-analysis of 32 cross-sectional studies demonstrated that pooled mean VO_{2peak} was 5.2 (95%CI 3.8 to 6.6) $ml.kg^{-1}min^{-1}$ lower in people ME/CFS vs. healthy controls.

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This study provided evidence that ME/CFS patients have a substantially reduced VO_{2peak} compared to controls which could increase their risk of all-cause mortality. However, there was insufficient data to ascertain the impact of peak exercise testing on ME/CFS symptoms in the days following testing.

A meta-analysis was conducted on studies which conducted repeat maximal exercise tests separated by 24h. The difference in work rate (WR) at anaerobic threshold (AT) (n=4) was -20.64 (95%CI -40.95 to -0.33)W in favour of controls, demonstrating that people with ME/CFS had a reduced power output at AT in the second of the two tests compared to apparently healthy controls. The effect size for this difference was large (d = -0.95) providing evidence that WR at AT effectively discriminates between ME/CFS and controls. These findings provide evidence of an objective and measurable response to repeat high intensity exercise which provides some evidence of a possible physiological element of the illness and may provide a potential objective marker in future studies.

In light of this evidence it was important to assess the effectiveness of exercise interventions in managing symptoms of fatigue in ME/CFS. Meta-analysis of studies assessing the effectiveness of graded exercise demonstrated that the pooled percentage difference for the overall effect (n=10) was -13.4% (95%CI -24.2 to -2.6) in favour of intervention. This indicates that exercise results in a clinically relevant reduction in fatigue. However, when studies using the Oxford Criteria case definition were removed from the analysis (n=5) the percentage difference reduced to -9% (95%CI -21.8 to -3.7). The findings indicate a

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degree of uncertainty around the effectiveness of exercise programmes in ME/CFS which would support evidence from survey data that graded exercise programmes may only be effective for a limited number of people with ME/CFS.

To explore this in more detail, in-depth interviews were conducted with six people with ME/CFS using an interpretive phenomenological analysis. Participants described feeling as though they are losing themselves and feel a lack of legitimacy about the hidden nature of the illness. Those with ME/CFS described 'battling' their illness which is not commonly cited in other chronic health conditions. Those with ME/CFS described wanting to be more active although this is contrasted with the unpredictability of the illness. People with ME/CFS described a desire for others to empathise and demonstrate understanding of their illness. Nevertheless, there was some evidence that when people with ME/CFS were able to engage in activities which had personal meaning this resulted in improvement in mood. Evidence indicated the potential for an activity management strategy in ME/CFS.

A new form a graduated physical activity was considered for people with ME/CFS. The proposed intervention is designed to be flexible in intensity and duration depending on the symptom profile of the individual and allow individuals to choose from a number of possible activities.

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List of abbreviations

BCW	Behaviour Change Wheel
Canadian criteria	Refers to Carruthers <i>et al.</i> (2003) diagnostic definition
CBT	Cognitive Behavioural Therapy
CDC	Centre for Disease Control and Prevention
CERT	Consensus on Exercise Reporting Template
CFQ	Chalder Fatigue Questionnaire
CFS	Chronic Fatigue Syndrome
CFS-APQ	Chronic Fatigue Syndrome – Activities and Participation Questionnaire
CI	Chronotropic Intolerance
CIS	Checklist Individual Strength
COM-B	Capability, Opportunity, Motivation, Behaviour
COREQ	Consolidated Criteria for Reporting Qualitative Research
FM	Fibromyalgia
FSS	Fatigue Severity Scale
GET	Graded Exercise Therapy
ICC	International Consensus Criteria (Carruthers <i>et al.</i> 2011)
IOM	Institute of Medicine Criteria
IPA	Interpretive Phenomenological Analysis
MCID	Minimal Clinical Important Difference
ME	Myalgic Encephalomyelitis
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MET	Metabolic Equivalent
MRC	Medical Research Council

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Oxford criteria	Refers to Sharp <i>et al.</i> (1991) diagnostic definition
OI	Orthostatic Intolerance
PAG	Patient Advisory Group
PEM	Post Exertional Malaise
PIS	Participant Information Sheet
PPI	Patient/ Public Involvement
POTS	Postural Orthostatic Tachycardia Syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
ROB	Risk of Bias
SAQOR	Systematic Appraisal of Quality for Observational Research
SE	Standard Error
SD	Standard Deviation
TDF	Theoretical Domains Framework
TSK	Tampa Scale of Kinesiophobia
VAS	Visual Analogue Scale
VCO ₂	Volume of carbon dioxide
VO ₂	Volume oxygen
VO _{2peak}	Peak Oxygen Uptake
95%CI	95% Confidence Interval
95%PI	95% Prediction Interval

Chapter 1: Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an illness characterised by unexplained recurrent persistent fatigue and a marked, rapid physical and/ or cognitive fatigability in response to exertion (Carruthers *et al.*, 2011). The symptoms of ME/CFS are severe enough to produce a substantial decrease in physical, social, or occupational activity (Collin *et al.*, 2011). Post-exertional malaise (PEM), cognitive dysfunction and disturbed or unrefreshing sleep are common symptoms for the majority of people with ME/CFS (Collin *et al.*, 2016).

At present, diagnosis is via a process of elimination and there is no consistent international diagnostic definition used within the literature, with at least 20 different diagnostic definitions currently in use (Brurberg *et al.*, 2014). Furthermore, the symptom profiles can vary between those with the illness. The severity of the illness can result in some maintaining relative levels of activity (approximately 50% of pre-illness levels) while others may be more severely affected, for example they may be bedridden and require assistance with basic bodily functions (Carruthers *et al.*, 2011; Johnston *et al.*, 2014).

A key characteristic of ME/CFS is PEM (Holtzman *et al.*, 2019). PEM in ME/CFS is an increase in the severity of symptoms following a physiological, cognitive or emotional stressor (Chu *et al.*, 2018). The onset of PEM symptoms can occur up to forty-eight hours following a stressor (Morris and Maes, 2013; Jason *et al.*, 2015) although this often occurs within twenty-four hours (Carruthers *et al.*, 2011). While the term 'malaise' may imply a slight discomfort

or fatigue, PEM is a debilitating relapse in symptoms including extreme fatigue (Cook *et al.*, 2017). Other terms used within the literature for this include post activity relapse (Morris and Maes, 2013), post exertional neuroimmune exhaustion (including post exertional exhaustion and post exertional symptom exacerbation) (Carruther *et al.*, 2011) and impaired recovery (Vermeulen *et al.*, 2010).

While PEM maybe triggered by a stressor which exceeds a particular threshold (Chu *et al.*, 2018). There is some evidence that if physical activity levels are kept below this threshold and then workload slowly increased over time, this could result in an overall improvement in symptoms (Wallman *et al.*, 2004; Moss-Morris *et al.*, 2005; White *et al.*, 2011). Interventions designed to manage ME/CFS through an incremental increase in exercise duration and intensity are known as graded exercise therapy (GET) (White *et al.*, 2011). However, the debate around the use of GET in the treatment of ME/CFS is contentious with patient groups, and some researchers and clinicians arguing that exercise interventions are not evidence based (Wilshire *et al.*, 2017) and may not only be ineffective but may also be harmful to those with ME/CFS (Twisk and Maes, 2009; The ME Association 2015; Geraghty *et al.*, 2019a).

The aetiology of ME/CFS remains unclear (Newton *et al.*, 2007) and there is no consistent evidence for a single biological cause (Moss-Morris *et al.*, 2005). As well as a lack of understanding about the cause of the illness there is currently little consensus about the maintaining factors of the condition (Carruthers *et al.*, 2011). Vercoulen *et al.* (1998) argued that ME/CFS is

maintained primarily through negative illness beliefs which results in a downward spiral of activity. Over time, people with ME/CFS develop the belief that they have an ongoing, serious and uncontrollable illness and that too much activity is harmful for symptoms, and that the only way to manage their illness is to reduce activity levels (Moss-Morris *et al.*, 2005). This theory underpinned the development of cognitive behavioural therapy (CBT) and GET interventions designed to encourage patients to increase activity levels without focusing on symptom cues (Harvey and Wessely, 2009; White *et al.*, 2011). However, critics of this model argue that ME/CFS is a complex condition and is unlikely to be maintained by behavioural responses alone and there is evidence of possible physiological mechanisms (Maes and Twisk, 2010). Indeed, research has demonstrated impaired cardiovascular responses to standing (Hollingworth *et al.*, 2010) and during exercise (Nelson *et al.*, 2019). Evidence has also indicated possible mitochondrial dysfunction (Tomas *et al.*, 2017; Missailidis *et al.*, 2019; Tomas and Elson, 2019) and a possible limited oxygen transport capacity (Vermeulen *et al.*, 2010).

There is an ongoing debate about the effects of exercise and physical activity interventions for the treatment of ME/CFS. It is well established that over-exertion for this group will cause a worsening of symptoms. Nevertheless, what is not clear is if exercise interventions can be used to effectively manage the condition. There is also continuing debate over the possible maintaining factors of the illness and how these are used in the development and implementation of interventions in the treatment of ME/CFS. It is therefore the

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aim of this thesis to explore the relationship between physical activity and ME/CFS.

Chapter 2: Literature Review

The terminology used for ME/CFS has varied. Including ME (Brurberg *et al.*, 2014), CFS (Holmes *et al.*, 1988; Fukuda *et al.*, 1994), CFS/ME (NICE, 2007), ME/CFS (Carruthers *et al.*, 2003; Carruthers *et al.*, 2011), and systemic exertion intolerance disease (SEID) (IOM, 2015). Although there is still debate over the label for the condition, many in the field advocate moving away from the term CFS (Carruthers *et al.*, 2011; IOM, 2015; Haney *et al.*, 2015) as there is a commonly expressed view that the term 'chronic fatigue syndrome' has led to negative perceptions on the part of clinicians and the public (IOM, 2015). There are also arguments that the term ME may also be inappropriate because of the general lack of evidence of brain inflammation in people with ME/CFS (Johnston *et al.*, 2014) as well as the less prominent role of myalgia in people with ME/CFS when compared to core symptoms (IOM, 2015).

It is also acknowledged that there are many who believe chronic fatigue, CFS and ME to be distinct, separate conditions (Twisk, 2019). Twisk (2018) stated that ME and CFS are two completely different concepts and that whilst muscle fatigability/prolonged post-exertional muscle weakness and specific neurological symptoms are discriminative features of ME, these are not required to meet the diagnosis for CFS (Twisk, 2018). However, others dispute that the assertion that CFS and ME are different clinical entities (Brurberg *et al.*, 2014). Whilst others report that ME/CFS represents a group of illnesses with a distinct biological aetiology with very similar phenotypes or sub-types (Gerwyn and Maes, 2017). Or a group of conditions on one continuum with no clear boundaries between them (Maes *et al.*, 2012). Nevertheless, in line with

the IOM (2015) report, for the purposes of this thesis the umbrella term ME/CFS is used throughout when discussing studies which have assessed CFS, ME, CFS/ME and ME/CFS.

2.1 Case definitions in ME/CFS

Another area of contention in the study of ME/CFS is the clinical diagnosis of the condition. The most commonly cited case definition of ME/CFS is Fukuda *et al.* (1994) (Brurberg *et al.*, 2014), commonly referred to in the literature as the 1994 CDC criteria for CFS. Although frequently cited, the Fukuda *et al.* (1994) case definition is polythetic (Sunnquist *et al.*, 2017), that is, that any combination of 4 symptoms from a possible 8, could fulfil the Fukuda *et al.* (1994) case definition. These 8 symptoms include, impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi joint pain, new headaches, unrefreshing sleep and PEM (Fukuda *et al.*, 1994). It is therefore possible that some individuals who meet this diagnostic criteria do not have symptoms which are now recognised as core indicators of the illness; such as PEM, memory/concentration problems, or unrefreshing sleep (Jason *et al.*, 2015).

This was demonstrated in a study by Collin *et al.* (2016) which assessed the symptom profiles of people with ME/CFS in a UK cohort containing 7,041 people and a Dutch cohort of 1,392 who were assessed for ME/CFS symptoms. This study reported 6 phenotypes based on 9 common symptoms in people with ME/CFS attending UK specialist services and replicated 3 phenotypes (based on 5 of these symptoms) in people with ME/CFS attending

a Dutch specialist service. From this analysis they reported that PEM, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms for both cohorts of ME/CFS. Although Collin *et al.* (2016) acknowledged that this may be a reflection of the diagnostic criteria used in both countries (Dutch individuals diagnosed with the Fukuda *et al.* (1994) criteria, UK diagnosed using NICE (2007)). The strengths of this study include a large sample size and the replication of its findings across two independent samples, one in the UK and one in the Netherlands. However, participants in the Dutch sample were required to remember their symptoms over the previous six months which could likely result in recall bias (Evans and Jason, 2015). This study also only included a limited number of symptoms (12) however it has been demonstrated that there may be 53 symptoms associated with ME/CFS (Johnston *et al.*, 2014). This study also does not consider the severity of symptoms which could impact on the symptom profile of individuals. Nevertheless, these findings add weight to the importance of these key symptoms in case definitions of ME/CFS.

Another commonly cited case definition within the UK, specifically in relation to GET interventions is the Oxford Criteria case definition (Sharpe *et al.*, 1991) for CFS. The Oxford Criteria case definition does not require PEM to be present in any form and therefore it is feasible that individuals who meet the Oxford Criteria may not meet other case definitions (Haney *et al.*, 2015). This raises questions about the population that was included as this case definition may include those who have other fatiguing conditions or may not have an illness.

This was supported by Baraniuk (2017) who reported in a study of 3,958 participants, 85% of Oxford-defined cases were inappropriately classified as ME/CFS. Findings from Baraniuk (2017) demonstrated that treatment studies based on Oxford criteria may be seriously flawed because they can potentially select a cross-section of the healthy general population. This is because healthy subjects with mild fatigue were selected and mis-labelled rather than providing a rigorously defined ME/CFS group. However, this study used a descriptive survey where participants self-reported symptoms and there was no assessment by a clinician to assess symptom type and severity and researchers were unable to verify exclusion criteria. This was demonstrated in a study by Strand *et al.* (2016) which assessed the effectiveness of the DePaul Symptoms Questionnaire which is based on the Fukuda *et al.* (1994), Canadian Criteria (2003) and ICC (2011) case definitions in assessing symptoms in people with ME/CFS. This study demonstrated that the use of self-assessment questionnaires was a useful symptom screening, but additional medical and psychological examinations are also needed in order to make a reliable diagnosis.

In response to these criticisms, other case definitions have been developed including the Canadian Criteria (Carruthers *et al.*, 2003), the International Consensus Criteria (ICC) (Carruthers *et al.*, 2011) and the Institute of Medicine (IOM) (2015). The core symptoms which are not required in previous case definitions, such as PEM (or post-exertional worsening of symptoms) and cognitive impairment, must be present to meet these case definitions (Sunnquist *et al.*, 2017). These definitions, such as the ICC (2011) and IOM

(2015) criteria, address some of the problems of the broad case definitions (Nacul *et al.*, 2017). However, these require a combination of specific symptoms for diagnosis, in addition to the presence of incapacitating chronic fatigue. For example, the IOM (2015) criteria requires PEM and unrefreshing sleep, and either cognitive impairment or orthostatic intolerance for diagnosis confirmation (Nacul *et al.*, 2017). While the Canadian Criteria and ICC (2011) require the combination of a larger number of symptoms indicating impairments in a number of proposed body systems (Nacul *et al.*, 2017).

To investigate the impact of different diagnostic definitions, Jason *et al.* (2013a) assessed patients with both the Fukuda *et al.* (1994) and the Canadian Criteria (2003) case definitions. This study evaluated three samples, one in the Chicago area of the United States, one from the SolveCFS BioBank in the United States and one in the Newcastle upon Tyne area in the United Kingdom. Using these three samples, the participants were then split into two groups. The first who met the Fukuda criteria were described as the CFS group. Those who met the Canadian Criteria were described as having ME/CFS. Consistent findings across the three data sets suggested that about three-quarters (77.2%, 72.7%, 72.9%) of those within the three samples met the case definition for ME/CFS (Canadian Criteria), whereas a larger group of patients (96.3%, 92.6%, 86.5%) were identified through the Fukuda *et al.* (1994) criteria. However, what is not clear from these findings is if the Canadian criteria is too specific and excludes those with the illness or if the Fukuda *et al.* (1994) criteria is too broad. Further still, as critics of the Fukuda *et al.*, (1994) criteria argue that this case definition may include those with

other fatiguing conditions, it would have been advantageous to understand the symptom profiles and severity of those who fulfil these different case definitions, although this was not addressed by Jason *et al.* (2003a).

To assess this, Johnston *et al.* (2014) considered the difference in symptoms severity between those who met the Fukuda *et al.* (1994) criteria against those who met the Canadian (2003) and the ICC (2011) case definitions for ME/CFS. For this study, participants completed a self-assessment of their symptoms from the previous 30-days alongside the SF-36 and WHO DAS 2.0 questionnaires. 41 participants completed the survey, 19 met the Fukuda *et al.* (1994) definition only, 5 met the Fukuda *et al.* and the Canadian criteria and 22 met the ICC (2011) case definition of ME/CFS. That is, 91% met the Fukuda *et al.* case definition, 60% met the Canadian and Fukuda *et al.* and 49% met the Fukuda *et al.*, (1994), Canadian and ICC case definitions. The findings from this study demonstrate that those who meet the ICC (2011) definition had substantially lower scores for SF-36 and greater scores for the WHO DAS 2.0 scales in all domains. This demonstrated greater disability and poorer social functioning and cognitive difficulties in those who met the ICC (2011) case definition. This study provides weight to the argument that these more recent case definitions identify a smaller and more disabled group. However, it is not clear if these are a sub-group with a greater severity of illness or the ICC (2011) diagnostic definition has greater sensitivity and specificity. Although, again this study relies on self-reported data from questionnaires and requires participants to recall symptoms from the previous 30 days. The sample of 41

is also limited and it is unclear if this study had adequate statistical power as this was not reported.

Brurberg *et al.* (2014) assessed the assertion that definitions such as the Canadian Criteria and ICC case definitions are more effective at conceptualising a specific neuro-immunological condition, assumed to be more severe and less psychologically attributed by other case definitions (Carruthers *et al.*, 2003; Carruthers *et al.*, 2011; Brurberg *et al.*, 2014). To assess this, Brurberg *et al.* (2014) conducted a systematic review investigating current diagnostic definitions used within the ME/CFS literature. In this review of 20 different case definitions, it was argued that none of the definitions included supported the hypothesis that some case definitions more specifically identify patients with a neuro-immunological condition. Further stating that the Canadian (2003) and ICC (2011) case definitions do not necessarily exclude patients with psychopathology. Although, Brurberg *et al.*, (2014) acknowledged that the quality of the included studies was weak, as they included a heterogeneous patient population across the included papers and for case definitions such as NICE (2007) there were no validation studies at the point of analysis.

The Oxford criteria is widely seen as the broadest case definition while the ICC (2011) case definition is recognised as the narrowest (Gerwyn and Maes, 2017). Nevertheless, no diagnostic approach has been shown to uniquely identify patients with a single illness as evidence by a common pathophysiology (Gerwyn and Maes, 2017). Currently it is argued that those

who received a diagnosis of ME/CFS should have symptoms of fatigue, PEM, sleep disturbances, with cognitive impairment and/or orthostatic intolerance (Haney *et al.*, 2015). Indeed, Haney *et al.* (2015) along with the IOM (2015) recommend no longer using the Oxford Criteria case definition for diagnosing ME/CFS as this differs from other case definitions and is the least restrictive and therefore the most likely to include individuals with other overlapping illnesses. However, studies assessing GET in ME/CFS based on case definitions such as the Canadian Criteria (2003), ICC (2011) or IOM (2015) are not available. A summary of the commonly cited case definitions can be found in table 2.1. For an overview of all case definitions for ME/CFS see Brurberg *et al.* (2016).

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Table 2.1; Summary of commonly used case definitions for ME/CFS used in this thesis

Reference	Sharpe <i>et al.</i> (1991)	Fukuda <i>et al.</i> (1994)	Carruthers <i>et al.</i> (2003)	Carruthers <i>et al.</i> (2011)	Institute of Medicine (2015)
Commonly referred to as	The Oxford Criteria	CDC (1994) Criteria*	The Canadian Criteria	The International Consensus Criteria (ICC, 2011)	IOM (2015)
Criteria for ME/CFS	<ul style="list-style-type: none"> - Severe and disabling fatigue ≥ 6 months which effects mental and physical functioning - may also have mood disturbances, myalgia and sleep disturbances 	<ul style="list-style-type: none"> - Fatigue ≥ 6months And 4 of the following - Impaired memory or concentration - sore throat - tender lymph nodes - muscle pain - multi joint pain - new headaches - unrefreshing sleep - PEM 	A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations. Fatigue ≥ 6 months.	A patient will meet the criteria for post exertional neuroimmune exhaustion (including PEM), at least one symptom from three neurological impairment categories, at least one symptom from three immune /gastro-intestinal /genitourinary impairment categories, and at least one symptom from energy metabolism/transport impairments	Patient required to have the following three symptoms: <ol style="list-style-type: none"> 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of activity ≥ 6 months and is accompanied by profound fatigue, and is not substantially alleviated by rest, 2. PEM 3. Unrefreshing sleep At least one of the two following also required: <ol style="list-style-type: none"> 1. Cognitive impairment 2. Orthostatic intolerance

*referred to in this thesis as Fukuda *et al.* (1994). Diagnostic definitions are used following exclusion of other possible causes. This is not an exhaustive list of case definitions. For an overview of other case definitions see Brurberg *et al.* (2014).

2.2 Prevalence and Recovery in ME/CFS

The large number of case definitions of ME/CFS has resulted in difficulty with attempts to estimate the prevalence of ME/CFS within the population. A study by Valdez *et al.* (2019) assessed the prevalence of ME/CFS in the United States (US). This study analysed individual records of people in the US health care system through a database named Optum. In this study records of approximately 50million individuals were assessed. The findings of this study estimate the prevalence of ME/CFS in the US to be between 519 to 1,083 per 100,000 (0.52% to 1.04%) or between 1.7 and 3.4 million people in the US. Although it should be noted that this sample only includes people who had health care insurance and there was no attempt to confirm diagnoses.

Lim *et al.* (2020) conducted a systematic review of 46 studies which assessed the prevalence of ME/CFS. Findings from their meta-analysis report that the pooled prevalence of ME/CFS in the population is 0.68% (Tau = 1.3) (95%CI 0.48 to 0.97) with high heterogeneity $I^2=99.4\%$. This review also provided results of prevalence by case definition; The Oxford Criteria (n=4) (1.41%, 95%CI 0.68 to 2.93), Fukuda *et al.* (1994) (n=34) (0.89%, 95%CI 0.60 to 1.33), Lloyd *et al.* (1990) (n=4) (0.79%, 95%CI 0.05 to 12.55) and Holmes *et al.* (1988) (n=8) (0.17%, 95%CI 0.06 to 0.49). Data was not provided in relation to studies using the Canadian, ICC or IOM case definitions. Findings from this review provides evidence of the prevalence of ME/CFS to be approximately 0.7%, although this varies depending on the case definition used. However, the meta-analyses on differing case definitions only contained a small number of studies and the review by Lim *et al.* (2020) did not use statistical methods

to mitigate against these small sample sizes. For example, methods such as Knapp and Hartung which estimates Tau using a t-distribution rather than a z distribution. This would have resulted in wider confidence intervals to provide a more accurate reflection of the uncertainty associated with these estimates (IntHout *et al.*, 2014).

As well as difficulty in establishing the prevalence of ME/CFS, differing case definitions and complexity with diagnoses have resulted in difficulty with establishing the recovery rate in people with ME/CFS. Tiersky *et al.* (2001) conducted a longitudinal study of 47 people with ME/CFS (35 people at follow-up) at two time points (range = 24–63 months between assessments). The case definitions of ME/CFS were Holmes *et al.* (1988) and Fukuda *et al.* (1994). Assessment of ME/CFS was made by a physician's assistant or nurse trained in diagnosing ME/CFS. This study reported that of the 35 people who attended follow-up, 97% of participants still had severe ME/CFS (defined as severe fatigue and at least 7 symptoms). Although this study was only conducted on a limited number of individuals and it is not clear how many of the 12 non-attendees at follow-up had shown signs of recovery. However, from this study there are two areas for consideration. Firstly, at 2 years participants still demonstrated significant illness and secondly, only a small number of people (1 from 35) reported a recovery. This study did report that 57% of the ME/CFS participants demonstrated improvement over time, whereas 43% did not, although the 57% still met the clinical diagnosis of ME/CFS.

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Joyce *et al.* (1997) conducted a review assessing the proportion of people with ME/CFS who report recovering from the illness. This review provided a summary of the included papers however did not attempt a quantitative synthesis of the data. This review reported that the outcome of ME/CFS in adults was of concern and that most people who were followed-up reported continued symptoms and disability. Although this study only summarised the findings from the papers rather than undertaking a meta-analysis to provide an overall pooled effect. This therefore limits the application of the phrasing, 'most people'. Nevertheless this review contributes to the argument that there is limited number of people with ME/CFS who report a 'recovery' from the illness. Of the 5 studies which assessed recovery in ME/CFS it was reported that <10% of people with a diagnosis of ME/CFS achieve pre-illness levels of functioning. Joyce *et al.* (1997) further argued that as the criteria for ME/CFS became more stringent the outcome became less favourable with 40% of those with chronic fatigue (but not a definition of ME/CFS) improved.

Cairns and Hotopf (2005) conducted a systematic review investigating the prognosis for those with ME/CFS, specifically assessing their rates of recovery. Findings from this review demonstrated that although the majority of people with ME/CFS do not report a full recovery, many report an improvement in symptoms and that for the 14 studies which used a case definition of ME/CFS, the median full recovery rate was 5% (range 0–31%). Although it is unclear how this overall statistic was generated as this review did not include a meta-analysis or an explicit overview of how study findings were synthesised which raises questions over the accuracy of the 5% value reported. At the time

of writing this thesis there are no updated studies which have used more accurate methods to synthesise data from the studies assessing recovery in ME/CFS. Although reviews provide evidence of a low recovery rate in ME/CFS the ambiguity used to summarise the statistics of ME/CFS makes it difficult to appreciate the clinical implications of these reviews. However, evidence would indicate that a relatively small number of people diagnosed with ME/CFS \leq 10% appear to report a recovery and achieving pre-illness levels of physical activity. Although in a narrative review by Vink and Vink-Niese (2019) it was argued that data appeared to suggest that people with ME/CFS adapt to their impairments instead of recover from them. Arguing further that that most of those who feel recovered from ME/CFS have stabilised at a lower level of functioning than that before their illness. Vink and Vink-Niese (2019) argues that consequently, even a recovery percentage as low as 5%, might well be too optimistic.

2.3 Theories relating to ME/CFS

2.3.1 The Cognitive Behavioural Model of ME/CFS

There is currently a lack of knowledge of the causal and maintaining factors of the illness, which may be in part due to the range of difference diagnostic case definitions used which creates difficulty in making comparisons across studies (Missailidis *et al.*, 2019). Nevertheless, in an attempt to provide an understanding of physical activity and ME/CFS two models have been developed. These are known as the cognitive behavioural model of ME/CFS (Vercoulen *et al.*, 1998; Clark and White, 2005; Harvey and Wessely, 2009; Geraghty *et al.*, 2019b) from which GET was developed. The second, the

energy envelope theory (Jason, 2008) of which pacing is closely associated. Although pacing was developed prior to the development of the energy envelope theory, pacing is often now described alongside this theory.

The cognitive behavioural model of ME/CFS (Vercoulen *et al.*, 1998; Clark and White, 2005; Harvey and Wessley, 2009) was developed on the principle that people with ME/CFS avoid physical activity because they have a belief that activity causes a worsening of symptoms (Vercoulen *et al.*, 1998). This avoidance behaviour results in a worsening of symptoms through deconditioning (Vercoulen *et al.*, 1998) which results in a pattern of behavioural and biological responses contributing to a prolonged severe fatigue syndrome (Harvey and Wessely, 2009). Harvey and Wessely (2009) stated that based on this model, the initial cause of the fatigue has a limited impact on the eventual course of the illness. Instead, it is the maintaining factors, such as dramatic fluctuations in levels of activity (so called 'boom and bust' cycles), that need to be addressed if recovery is to occur (Harvey and Wessely, 2009). The possible mechanisms of the illness could be either directly through reduced physical strength and cardiovascular deconditioning or indirectly through the physiological consequences of inactivity (Clark and White, 2005). Such impairments lead to symptoms at a lower level of physical activity (Clark and White, 2005). The inability to function at previous levels may lead to frustration, low mood and a lack of motivation and lethargy (Clark and White, 2005). Clark and White (2005) argue that this creates 'a vicious cycle' of increased exercise avoidance and subsequent symptoms occurs, which serves to perpetuate fatigue and therefore ME/CFS.

However, critics of this model argue there is mounting evidence that its use has resulted in an incorrect view of the illness by health care professionals (Geraghty and Blease, 2019). For example, pain is a common symptom in ME/CFS however supporters of the cognitive behavioural model argue that pain is a consequence of overly focusing on body sensations (Geraghty *et al.*, 2019b). This has contributed to a large proportion of people with ME/CFS feeling disbelieved and distressed following medical encounters particularly in response to treatment approaches which many view as inaccurate and stigmatising (Geraghty and Blease, 2019). In a narrative review by Geraghty and Blease (2019) they argued that this model propagates a flawed view that ME/CFS is heavily influenced by the individuals' psychological status. Further arguing that it indirectly blames the individual for perpetuating their illness and asserts that those with ME/CFS can end the illness if they were to only engage in therapies such as CBT and GET (Geraghty and Blease, 2019; Geraghty *et al.*, 2019b). This model creates a perception that ME/CFS is an illness of mind-body, something that can be cured by positive thinking and this rhetoric may be partly responsible for influencing the way in which doctors and health professionals perceive the illness (Geraghty and Blease, 2019).

The views held towards ME/CFS in health care professionals was assessed in a systematic review of 21 qualitative studies by Bayliss *et al.* (2014). This study reported that scepticism among health professionals about the status of ME/CFS can sometimes lead to reluctance in making a diagnosis. Further arguing that there was evidence that some general practitioners (GPs) provide a psychological label such as depression in order to avoid saying that their

diagnosis is 'uncertain'. Other health professionals hold a "somatisation" model of illness where patients are thought to be expressing social and emotional problems in physical symptoms (Bayliss *et al.*, 2014). Finally, Bayliss *et al.* (2014) stated that this can be experienced by people with ME/CFS as a blame shifting device with people with ME/CFS feeling held accountable for their poor health. Bayliss *et al.* (2014) argued that greater use of the biopsychosocial model would improve diagnosis and management of ME/CFS. As a focus by some health care professionals on a biomedical approach can lead to their conclusion there is no real illness as there is no current identifiable pathology (Bayliss *et al.*, 2014).

2.3.2 The Energy Envelope Theory

Supporters of the cognitive behavioural model of ME/CFS advocate that the physiological deconditioning associated with ME/CFS can be reversed if an individual is willing to gradually exceed their perceived energy limits through recondition of their bodies through GET (Clark and White, 2005). However, in contrast to this approach, Jason (2008) proposed the Energy Envelope Theory. The Energy Envelope Theory states that to manage ME/CFS symptoms effectively, expended energy levels should remain within the "envelope" of perceived energy levels (Jason, 2008). People with ME/CFS can then sustain this level of physical and mental functioning while reducing symptom severity and the frequency of relapses more efficiently (Jason, 2008).

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Jason (2008) conducted an observational study with 110 participants with ME/CFS. They were required to grade their perceived energy (their estimation of their available energy resources) as well as their expended energy (their estimation of the total amount of energy exerted) over 24 hrs on a 0-100 scale. Where 0 meant no energy and 100 meant an abundance of energy. Using these two tools, a participant's percentage of available energy was calculated by dividing the participants' expended energy by their perceived energy and multiplying by 100. If a participant scored less than 100 this meant they had energy left, over 100 meant they had used more energy than available. The results ranged from 50% to 5,667% with a mean percentage available energy of $339 \pm 685\%$. This study also reported a correlation with perceived available energy and measures of functioning, including depression, anxiety, fatigue, pain, quality of life, and disability. Findings from this study found that daily energy quotient was related to several indices of functioning, including depression, anxiety, fatigue, pain, quality of life, and disability. Jason (2008) further stated that the energy envelope theory, was an applicable construct for ME/CFS.

However, this study is based on self-reported data only and Evering *et al.* (2011) reported that people with ME/CFS under reported their physical activity levels and therefore the reliability of self-reported data is unclear. This study also asked participants to score their perceived available and spent energy levels, which is a novel question and it is not clear how the participants themselves interpreted this and what information they used to make their decisions. Jason (2008) did not report any use of habituation within this study,

which may have been helpful to allow participants to become acquainted with the measurement tools. Although Jason *et al.* (2013b) and Jason *et al.* (2009) state that the energy envelope approach helps patients pace activities and manage symptoms and can significantly improve their quality of life.

A number of studies demonstrate that pacing appears to be beneficial in managing symptoms in ME/CFS (Nijs *et al.*, 2009; Goudsmit *et al.*, 2012; The ME Association 2015; Kos *et al.*, 2015). Yet pacing does not allow for an increase in total activity levels and instead is a strategy to manage energy levels to reduce the occurrence of 'boom and bust' cycles. The available evidence appears to support the energy envelope theory as an appropriate model for understanding energy levels in ME/CFS. However, the concept of maintaining energy levels '*within the envelope of perceived energy*' is at odds with Clark and White (2005) argument that for someone with ME/CFS to be '*released from their self-perpetuating cycle of inactivity*' they should exceed their perceived energy limits. This provides two contrasting views of the management of physical activity in ME/CFS and from these two theories, two different approaches to its management; pacing and GET.

2.4 Fear of physical activity in ME/CFS

Vercoulen *et al.* (1998) argued that people with ME/CFS are highly sensitive to bodily symptoms and interpret these as a signal that there is something wrong with their body (Vercoulen *et al.* 1998), as well as an abnormal perception of effort (Clark and White, 2005). It is argued that it is these beliefs that contribute to the reduction in physical activity in people with ME/CFS due

to a fear that activity will cause a worsening of symptoms (Clark and White, 2005). Kinesiophobia is defined as 'excessive, irrational and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury' (Silver *et al.*, 2002).

A study by Silver *et al.* (2002) supported the argument that rest and avoidance of activity whilst advantageous in the short term, are maladaptive in ME/CFS in the long term due to deconditioning. In their study of 33 people with ME/CFS, participants were asked to complete the Tampa Scale of Kinesiophobia (TSK) before completing an exercise task on a cycle ergometer on a self-selected pace and given the instruction to 'ride as long as they felt able'. Heart rate, RPE (6-20) and concern over symptoms were recorded on a visual analogue scale (VAS). Work rate and measures of oxygen (VO_2) and carbon dioxide (VCO_2) were not measured.

Results from Silver *et al.* (2002) demonstrated that beliefs about illness were a bigger predictor of performance (i.e. total distance travelled) than physical symptoms, physical disability, mood and illness perception. It was also reported that Kinesiophobia accounted for 15% in the variance in distance cycled although the specific data relating to distance cycled is not presented in the paper. Silver *et al.* (2002) further argued that those with ME/CFS may hold dysfunctional avoidance beliefs that physical activity maybe unsafe for a person with ME/CFS. However, this study provided no objective measure of work load other than total distance cycled. It may also be the case that those with ME/CFS have a legitimate concern that activity will make their symptoms

worse and it is unclear how this was identified as the causal factor for performance. Finally, the TSK was designed to assess pain related fear of movement and there is a lack of clarity with regards to the appropriateness of this tool for people with ME/CFS. Whilst attempts were made by Silver *et al.* (2002) to modify this tool, this involved changing the word pain to fatigue however fatigue may not be the only, or main debilitating symptom of the condition (Nijs *et al.*, 2004a).

Nijs *et al.* (2004a) explored Kinesiophobia in 40 people with ME/CFS who had a clinical diagnosis of ME/CFS using the Fukuda *et al.* (1994) case definition. This study involved using a modified version of the TSK which used the phrasing 'symptoms' as oppose to 'fatigue' or 'pain' as these were believed to be more relevant to the ME/CFS population. Participants were required to complete the modified TSK before completing a $\text{VO}_{2\text{peak}}$ test on a cycle ergometer. This study reported that a proportion (65%) of those with ME/CFS demonstrated a fear of activity when measured using the modified TSK however there was no correlation with Kinesiophobia and the ability to reach maximum effort during a maximal exercise test (defined in this study as achieving 85% of age predicted maximum heart rate ($220 - \text{age}$) and a respiratory exchange ratio (RER) ≥ 1.0).

A study by Nijs *et al.* (2004b) assessed the relationship between Kinesiophobia, exercise capacity and disability in 64 people with ME/CFS diagnosed according to the Fukuda *et al.* (1994) case definition. This study required participants to complete a modified version of the TSK (Nijs *et al.*,

2004a) and the Chronic Fatigue Syndrome – Activities and Participation Questionnaire (CFS-APQ). Participants were then required to complete a maximal exercise test on a cycle ergometer until exhaustion. Maximal effort was defined as a heart rate $\geq 85\%$ age predicted maximum and RER ≥ 1.0 . However, Nijs *et al.* (2004b) reported that their findings did not support the theory that Kinesiophobia is associated with disability in people with ME/CFS, Nijs *et al.* (2004b) further question the clinical importance of Kinesiophobia in ME/CFS, as fear of physical activity/ exercise did not impair cardiovascular fitness.

To assess Kinesiophobia in ME/CFS further, Gallagher *et al.* (2005) conducted a study where physiological arousal in anticipation and during an exercise challenge was measured. The theory being that if people with ME/CFS had a fear of physical activity or exercise they would demonstrate an abnormal physiological response to this stressor. 42 people with ME/CFS who met the Oxford case definition, of which 24 (57%) also met the ICC (2011) case definition, were compared against 42 age, sex, social class and BMI matched healthy sedentary controls. Participants were tested over two days. Day one was a control session where data was collected 'on an ordinary day' and on day 2 participants exercised on a treadmill. Although it is not clear how long the exercise bout lasted and what the criteria for the end point of the exercise test were. Heart rate and galvanic skin response (GSR) tests were used to measure arousal, prior to exercising, during and after. This study reported that there was no evidence of exercise phobia, specifically there was no increase in symptomatic anxiety, GSR or heart in anticipation or in response to exercise.

This study also reported that activity levels were similar leading up to testing and there was no evidence of activity avoidance in the ME/CFS group. However, this study did report that the ME/CFS group spent less time on the treadmill and there was evidence that the ME/CFS group found the exercise task more challenging than controls.

Based on the findings of Gallagher *et al.* (2005) and Nijs *et al.* (2004a) there is limited evidence to support the theory of activity avoidance in ME/CFS, although these studies did not assess Kinesiophobia in different sub-groups of ME/CFS. Jones *et al.*'s (2012) study of repeat maximal voluntary contraction (MVC) assessed by 3x180 second isometric plantar flexion contractions reported that a proportion of the group demonstrated some form of exercise avoidance. This was measured by phosphor-creatine depletion, and did not appear to be a consequence of pain or fatigue. The study did not report how many of the 18 participants demonstrated exercise avoidance behaviours and of note, those who demonstrated this avoidance behaviour believed they had 'tried hard'. These findings would add support to a form of activity avoidance in a sub-group of ME/CFS which may account for the variability in findings in previous studies. It is also feasible that any avoidance of behaviour is not a maintaining factor of the illness and instead a rational response to feeling apprehensive of PEM (Newton *et al.*, 2011; Geraghty *et al.*, 2019b).

2.5 Physical activity and ME/CFS

It has been stated that those with ME/CFS may decrease their activity levels to manage their illness (Clark and White, 2005). It is important to understand

the activity levels in people with ME/CFS as a decrease in physical activity could be associated with increased risk of morbidity and mortality (Laukkanen *et al.*, 2016). A systematic review by Evering *et al.* (2011) compared the findings of 17 studies that assess the physical activity levels of people with ME/CFS. This review included studies which assessed activity levels in people with ME/CFS and apparently healthy controls using objective measures or subjective measures of physical activity. This review found that 14 studies, including 18 comparisons, showed a statistically lower level of physical activity in people with ME/CFS when compared with controls. Results also demonstrated that people with ME/CFS participated on average at approximately 68% of the activity levels of controls. This study further reported that when subjective measures of physical activity were used, studies were more likely to report statistical significant findings in the level of physical activity than when reporting the findings of objective measures (92% compared with 70%). Finally, this study also reported that of the 14 different measurement tools used to assess physical activity in ME/CFS, the validity and reliability of these outcome measures was only reported in seven.

There are a number of limitations to the findings from Evering *et al.* (2011). Firstly, the review provides no information about the comparison groups used in these studies as well as information relating to matching. The inclusion criteria stated that there needed to be an asymptomatic comparison however no other information was given. It is therefore not clear if the comparison groups are appropriate to compare against the ME/CFS group. Secondly, although this study conducted a meta-analysis of 7 out of the 17 studies, it

primarily focused on providing a narrative overview of their findings, for example 14 studies demonstrated a statistically significant difference between groups and provided no overall pooled difference in activity levels. Nevertheless, these findings provide evidence of reduced physical activity levels in people with ME/CFS and there may be a discrepancy between objective and subjective measures of physical activity.

Newton *et al.* (2011) conducted a cohort study of 107 people with ME/CFS diagnosed using the Fukuda *et al.* (1994) case definition. These were compared against 107 age, sex, and body mass index (BMI) matched controls who did not take part in regular exercise (<30 min exercise three times per week). Physical activity was measured over 7 days using accelerometry. This study reported that ME/CFS was not associated with higher levels of sedentary behaviour but reduced levels of moderate and vigorous activity. Further adding that moderate physical activity was reduced by 30% in ME/CFS compared with controls. Overall this study reported that physical activity levels in the ME/CFS group were low when compared to controls (79% ME/CFS vs. 47% controls not achieving 10,000 steps/ day). However, Newton *et al.* (2011) argued that their findings suggested people with ME/CFS move the same amount as people without ME/CFS. However, the intensity of the activity is reduced. Newton *et al.* (2011) further argued that it is possible that the reduction in physical activity intensity did not relate to the motivation to be physically active, instead a functional deregulation in the muscle or autonomic function. This study had a number of strengths including the time period of 7 days, which Evering *et al.* (2011) stated was the minimum duration required for effective

measurement of activity, as well as the matching for BMI and stipulating an activity level of controls add to the strength of the findings. Evering *et al.* (2011) and Newton *et al.* (2011) provide evidence of decreased physical activity levels in ME/CFS, however, it is unclear if these reduced levels of physical activity are associated with any increase risk of morbidity and mortality.

A Reduction in physical activity has been shown to be associated with a reduction in VO_{2peak} (Aspenes *et al.* 2011) which is associated with an increased risk of all-cause mortality (Laukkanen *et al.*, 2016). The association between VO_{2peak} and all-cause mortality were discussed in Lee *et al.* (2010) which stated that greater cardiorespiratory fitness, of which VO_{2peak} quantifies (Cortesse, 2020) improves insulin sensitivity, blood lipid and lipoprotein profile, body composition, inflammation, blood pressure and the functioning of the autonomic nervous system. Cardiorespiratory fitness was described by Cortesse (2020) as the ability of the cardiorespiratory system to supply oxygen to the muscles during physical activity and involves numerous bodily systems, (Glynn and Fiddler, 2009). These include; pulmonary ventilatory activity, gas exchange between alveoli and the blood, systolic and diastolic blood pressure, ventricular-arterial coupling, the capacity of the circulatory system to transport oxygen from the heart to the tissues and finally, the ability of muscle cells to extract and use oxygen, as well as the removal of waste products (Cortese, 2020). Cortesse (2020) argued that this reflects the global health of the body and Lee *et al.* (2010) stated that cardiorespiratory fitness was a surrogate measure of functional status of respiratory, cardiovascular and skeletal muscle systems. Cardiorespiratory fitness is a modifiable factor and it is well

established that exercise training substantially improves fitness and that fitness is associated with a reduction in all-cause mortality (Aspenes *et al.*, 2011).

Tikkanen *et al.* (2018) assessed the relationship between fitness, physical activity and cardiovascular disease in 502,635 adults. This study reported that fitness and physical activity demonstrated negative associations with a number of diseases including, coronary heart disease, cardiovascular disease, stroke and heart failure. Tikkanen *et al.* (2018) further reported that among all measures of fitness and physical activity, accelerometry-based physical activity showed the strongest inverse association for the risk of premature death. Finally this study reported an inverse associations of grip strength and cardiorespiratory fitness with coronary heart disease and arterial fibrillation being seen in each category of genetic risk, indicating that maintaining good fitness can compensate for genetic risk of these diseases. Although the authors reported that the sample, which was recruited through the UK BioBank, may have a bias towards healthy volunteers when compared the UK population as a whole.

A number of studies have assessed differences in VO_{2peak} between people with ME/CFS and healthy controls (Sisto *et al.*, 1996; LaManca *et al.*, 2001; Togo *et al.*, 2010; Robinson *et al.*, 2010; Ickmans *et al.*, 2013) however due to varied findings, it is not clear if there is a reduced VO_{2peak} in people with ME/CFS. Nijs *et al.* (2011) conducted a systematic review assessing differences in physiological outcomes during maximal exercise testing

between people with ME/CFS and apparently healthy controls. Nijs *et al.* (2011) included 15 studies and concluded that there was conflicting data in relation to VO_{2peak} in people with ME/CFS, but from the available data it appeared that physiological exercise capacity in ME/CFS is reduced. However, the study by Nijs *et al.* (2011) only provided a narrative description of the findings from these studies (3 studies found a statistically significant difference vs. 6 that did not) and did not attempt to synthesise these findings using a meta-analysis to produce an overall pooled effect. Using a meta-analysis would allow for a calculation of an effect size which includes all of the effects in a single summary statistic rather than relying on individual p-values which are driven by the size of the study (Borenstein *et al.*, 2009). Further assessment of any difference in VO_{2peak} between people with ME/CFS and controls would be beneficial in understanding this population.

2.6 Effects of physical activity on symptoms of ME/CFS

2.6.1 Cognitive dysfunction

Cognitive complaints are another common symptom, reported in up to 85% of people with ME/CFS (DeLuca *et al.*, 2004). Cognitive difficulties have been described as one of the more disabling and troubling symptoms of the illness (Tiersky *et al.*, 2001). A study by Cook *et al.* (2005) assessed the differences in cognitive performance between subjects with ME/CFS alone (Fukuda *et al.*, 1994) and ME/CFS with fibromyalgia (FM) and healthy sedentary adults. Subjects were initially VO_{2peak} tested before being split into two groups; an exercise group and a non-exercise group. The initial VO_{2peak} test took place two weeks prior to testing. The exercise group were required to cycle at 40%

of their VO_{2peak} for 20 minutes. Automated neuropsychological assessment matrices (ANAM) were used to assess cognitive performance, including; simple reaction time, running memory, memory recall, math processing, and matching to sample. The results of this study demonstrated that people with ME/CFS display significant cognitive deficits compared with healthy sedentary controls. However, this study reported that there was no effect of acute exercise on any cognitive variable, indicating that the differences were stable over time and not improved or impaired by 20 minutes of low to moderate physical exertion when compared to rest.

However, the sample size in this study was relatively small (ME/CFS 9 exercise, 11 rest vs. control 14 exercise, 12 rest). It may also have been that the exercise intensity of 40% of VO_{2peak} was too low to illicit any impairment. Stevens *et al.* (2018) stated that exercise intensities which remain below the anaerobic threshold may not result in PEM symptoms. Neary *et al.* (2008) demonstrated that when 6 people with ME/CFS exercised to exhaustion they exhibited significant exercise intolerance, reduced prefrontal oxygenation and reduced total blood volume response when compared with 8 healthy controls. Neary *et al.* (2008) argued that the altered cerebral oxygenation and blood volume may contribute to the reduced exercise load in ME/CFS and supports the contention that ME/CFS, in part, is mediated centrally. Robinson *et al.* (2019) stated that when comparing 48 people with ME/CFS (Fukuda *et al.*, 1994) against normative data, a slowing in basic processing speed was demonstrated. Further adding that impaired autonomic control of heart-rate is associated with reductions in basic processing speed.

2.6.2 Physiological responses to physical activity

Tomas and Elson (2019) argued that mitochondrial dysfunction may be a possible cause of the fatigue in ME/CFS. In this theory, it is argued that when people with ME/CFS are involved with repeated exercise, aerobic metabolism cannot be maintained and there is a shift to anaerobic metabolism to fulfil energy demands. This causes a subsequent build-up of lactate and reduction in pH (Tomas and Elson, 2019). A number of small studies have been conducted assessing VO_{2peak} in two maximal effort tests separated by 24hrs (VanNess *et al.*, 2007; Vermeulen *et al.* 2010; Snell *et al.* 2013; Hodges *et al.* 2017; Nelson *et al.* 2019; Lien *et al.* 2019). To date, research evidence from these studies has been contradictory with only few studies reporting a reduction in VO_{2peak} at test 2 compared with test 1 (VanNess *et al.*, 2007; Vermeulen *et al.*, 2010). However, the assessment of maximum effort in these studies is not adequately reported and it is unclear if all participants did indeed achieve their physiological maximum in both tests.

Lien *et al.*, (2019) also demonstrated an elevated blood lactate at the start of the second test, as well as the lactate threshold occurring at a lower VO_2 in people with ME/CFS in test 2 compared to test 1 which did not occur in the control group. However, there has only been a limited number of studies on this topic and sample sizes of these studies was small which reduces the precision of these findings. It should also be noted that these studies recruited people with ME/CFS who were willing to participate in multiple maximal effort tests. Due to this, it is possible that the samples included in these studies is a more active sub-group of the population. Finally, these studies provide

information about how people with ME/CFS respond to repeated exercise, they do not provide data on the causal factors of this and therefore it is only possible to hypothesise about the possible interacting factors. However, these studies all reported a reduced work rate at anaerobic threshold compared to healthy controls. This reduction in work rate in people with ME/CFS at the anaerobic threshold requires further exploration and may provide useful information in the field of ME/CFS.

Davenport *et al.* (2019) discussed the possible impact of chronotropic intolerance (CI) in ME/CFS. CI is described in Davenport *et al.* (2019) as a range of possible symptoms including; failure to achieve age-predicted maximal heart rate, delays in achieving age-predicted maximal heart rate, inadequate heart rates at submaximal workloads, slowed post-exertion recovery heart rate or heart rate fluctuations. This research group argue that people with ME/CFS have an abnormal heart rate response to exercise and they are unable to achieve above 80-85% age predicted maximum heart rate ($220 - \text{age}$). This study conducted a meta-analysis on 36 studies and reported that control subjects performed at 94.0% of age-predicted maximum heart rate (95%CI 93.6 to 94.4%), while individuals with ME/CFS performed at 82.2% (95%CI 81.9 to 82.5%) of age-predicted maximum heart rate. The difference (11.8%) had a large effect size (Cohen's d) -1.37 (95%CI -1.46 to -1.26). However, this study estimated age predicted maximum heart rate using each study's mean age ($220 - \text{mean sample age}$) which raises questions about the accuracy of these findings. Hodges *et al.* (2020) reported a proportion of their sample demonstrated evidence of CI however this was not consistent across

all participants with ME/CFS. Further investigation of CI may be beneficial in future studies.

2.7 Graded Exercise Therapy and ME/CFS

There have been a number of studies which have assessed the effectiveness of graded exercise therapy (GET) (Fulcher and White, 1997; Wearden *et al.*, 1998; Moss-Morris *et al.*, 2005; Wearden *et al.*, 2010; White *et al.*, 2011), in reducing symptoms of fatigue, improving quality of life and improving cardiovascular fitness using a VO_{2peak} test (Moss-Morris *et al.*, 2005) or a 6 minute walk test (Broadbent *et al.*, 2018). These studies, with the exception of Jason *et al.*, (2005) report that GET is effective in reducing symptoms of fatigue as well improving quality of life. These studies also state that GET is a safe treatment for those with ME/CFS with very few adverse events (White *et al.*, 2011). These findings were supported in a Cochrane systematic review and meta-analysis by Larun *et al.* (2019) which concluded that GET “probably” reduces fatigue at end of treatment (SMD -0.66) yet there was uncertainty about the risk of adverse events as this data was only provided in one study.

Although this review combined the standardised mean difference for each study in their meta-analysis which may introduce heterogeneity that is unrelated to any real between study difference (Hopkins, 2018). This review reported its findings in relation to a minimal clinically important difference (MCID) (7%) however this threshold relates to the 11-item Chalder Fatigue Questionnaire (CFQ) and there were 4 other fatigue scales used in the included studies in this meta-analysis. This review also included a number of

studies which used the Oxford Criteria case definition and the review did not consider the impact of excluding these studies from their review which is recommended by the IOM (2015).

White *et al.* (2011) conducted an RCT involving 641 people with ME/CFS diagnosed using the Oxford Criteria case definition, referred to as the PACE trial. This study compared adaptive pacing therapy (APT) (n=160), a form of pacing developed by the researchers, cognitive behavioural therapy (CBT) (n=161), GET (n=160), and specialist medical care (SMC) (n=160). The intervention lasted 24 weeks however there is little information about how the starting intensity and decision rule for progression. The study only states that after an initial baseline was decided there was '*a negotiated, incremental increase in the duration of time spent physically active*'. The outcome measures were the 11-item Chalder fatigue questionnaire (score 0-33) and the SF-36 (0-100). This study reported that fatigue was 3.2 points lower (10%) in GET compared to SMC and concluded that GET added to SMC results in a moderately improved reduction in fatigue in people with ME/CFS.

There are a number of limitations of this study, including the use of the SF-36 (range 0-100), where a higher score indicated better function. Participants could be recruited with a score of 65 however the researchers deemed a score of 60 or over as being within a normal range for the population. This means that a participant could have been recruited as ill enough to be in the studies inclusion criteria, while simultaneously being defined as well enough for the main outcome. Studies assessing GET in ME/CFS such as White *et al.* (2011),

Fulcher and White (1997), Powell *et al.* (2001), Wearden *et al.* (1998) and Wearden *et al.* (2010) used the Oxford Criteria case definition to assess for ME/CFS. While Moss-Morris *et al.* (2005) and Kos *et al.* (2015) used the Fukuda *et al.* (1994) case definition. Yet both the Fukuda *et al.* (1994) and the Oxford Criteria case definition have been criticised in the literature as both can result in a diagnosis of ME/CFS without the presence of PEM. PEM is often considered a core symptom of ME/CFS (Collin *et al.*, 2016) yet the Oxford Criteria case definition does not require PEM to be present in any form. It is therefore feasible that patients who would meet the Oxford Criteria may not meet other case definitions (Haney *et al.*, 2015), which raises questions about the patient group as this may include those who have other fatiguing conditions or may not have an illness.

A number of studies are critical of GET in ME/CFS (Twisk and Meas 2009; Vink and Vink-Niese 2008; Geraghty *et al.*, 2009), arguing that the evidence for its effectiveness is limited and survey data indicates a large proportion (74%) of respondents with ME/CFS state they felt worse following GET (Geraghty *et al.*, 2019a). Although this contradicts the findings from experimental studies (Fulcher and White 1997; Powell *et al.*, 2001; Moss-Morris *et al.*, 2005) which report that GET is beneficial in reducing fatigue in ME/CFS. Further exploration of incremental exercise and ME/CFS is another important area to assess the impact of activity and ME/CFS.

Summary of Chapter 2

It is widely accepted that PEM is a key symptom of ME/CFS. Nevertheless, the two commonly used diagnostic definitions; Fukuda *et al.* (1994) and the Oxford criteria case definitions do not require PEM as a core symptom to meet their definition of the illness. Critics argue that this has resulted in some individuals being diagnosed with ME/CFS who do not have a number of key symptoms such as PEM, unrefreshing sleep, cognitive dysfunction and OI and therefore may have a form of chronic fatigue but may not have ME/CFS. It is argued that definitions such as the Canadian (2003), ICC (2011) or IOM (2015) case definitions identify a smaller, more disabled group, although it is not clear if these definitions exclude people with the illness. However, to date the Fukuda *et al.* (1994) case definition of ME/CFS is the most commonly used diagnostic definition within this field of research. Further still, the Oxford Criteria, often described as the broadest case definition, has been used in a number of studies investigating GET in ME/CFS.

Evidence has shown that people with ME/CFS have reduced physical activity levels when compared to healthy controls. It has also been shown that reduced activity levels have been associated with a decrease in peak oxygen uptake (VO_{2peak}), an independent predictor of all-cause mortality. A number of studies have assessed VO_{2peak} in ME/CFS however there has only been a limited attempt to synthesise this data and to date these findings have not been discussed in relation to a clinically relevant threshold.

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There appears to be increasing evidence of measurable physiological outcomes during repeated maximal exercise tests, which appear in people with ME/CFS but not in controls. These outcomes may provide some evidence to support a possible physiological component of the illness which may provide limitations of the cognitive behavioural model of ME/CFS. If supported, this could also provide evidence for an objective marker for ME/CFS to aid in diagnosis.

GET in ME/CFS is a contentious topic with research evidence demonstrating an improvement in symptoms of fatigue in ME/CFS. Yet survey data indicates that GET may only be beneficial for a limited number of people with ME/CFS. The existing meta-analysis on this topic contains a number of methodological weaknesses such as inconsistencies in the data reported in one study and the data that has been meta-analysed. This review also converted the data in the included studies to standardised mean difference which may increase heterogeneity. There are a number of included studies which have used the Oxford Criteria case definition for diagnosis which may result in the sample containing people with other fatiguing conditions.

Finally, research investigating exercise interventions provide some evidence that this is an effective strategy for managing CFS/ME symptoms, however this is not universally accepted by patient groups. It is important to assess these interventions to understand why these may not be acceptable to a large number of patients. Discussions with patients may also provide an important

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insight into understanding if they would want to increase their activity levels and if so, what is beneficial and what is harmful. Ultimately, can a physical activity programme be developed that would increase physical activity levels without exacerbating symptoms that would be acceptable to this patient group?

Chapter 3: Aims and objectives

The aim of this thesis was to explore the relationship between physical activity and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Specifically, this thesis assessed if there was any reduction in the upper limit for relatively sustainable energy expenditure by assessing the difference in peak oxygen uptake (VO_{2peak}) in people with ME/CFS compared to apparently healthy controls. The impact of repeated VO_{2peak} tests was also explored to assess how post exertional malaise impacted on physiological measures.

This thesis then explored incremental exercise programmes in ME/CFS to critically consider the effectiveness of current interventions in reducing fatigue. A qualitative study was then conducted to provide insight into how people with ME/CFS perceive the role of physical activity and their illness. Using the data derived from this thesis, physical activity as a treatment was considered and a proposed physical activity intervention was developed.

The objectives for this thesis were:

1. To assess the extent of the difference in peak oxygen uptake in people with ME/CFS compared to apparently healthy controls.
2. To quantify the variability in 24-hour repeated maximal exercise tests of peak oxygen consumption in ME/CFS versus apparently healthy controls
3. To explore the experiences of physical activity/ exercise in people with ME/CFS using interpretive phenomenological analysis

4. To develop an intervention to aid in the management of symptoms and physical activity in people with ME/CFS

Chapter 4: Overall Framework for Thesis

This thesis aims to assess current evidence in the domain of physical activity and ME/CFS. The overall purpose of which is to explore the effectiveness of interventions to manage symptoms of ME/CFS as well as investigate the possibility of creating a new form of physical activity management intervention. The approach set out by the MRC (2006) guidance on developing and evaluating complex interventions was used to underpin this thesis, as well as the guidance by O'Cathain *et al.* (2019) on developing complex interventions. Critics of the MRC guidance argue that there is little information on how to progress through the early phases of the MRC in considering the key tasks in optimising an intervention (Michie *et al.*, 2008). Nevertheless, this framework was used in the development of this thesis and the following stages were followed:

1. *'Identifying the evidence base You should begin by identifying the relevant, existing evidence base, ideally by carrying out a systematic review'* (MRC, 2006)

The first stage of this thesis (chapters 5, 6 and 7) includes three systematic reviews and meta-analyses. The first assessed if there was a reduction in VO_{2peak} in ME/CFS vs apparently healthy controls. The second, assessed the impact of repeated maximal exercise tests on physiological measures both at peak exercise and the anaerobic threshold. The third assessed the effectiveness of incremental exercise interventions for reducing symptoms of fatigue in ME/CFS.

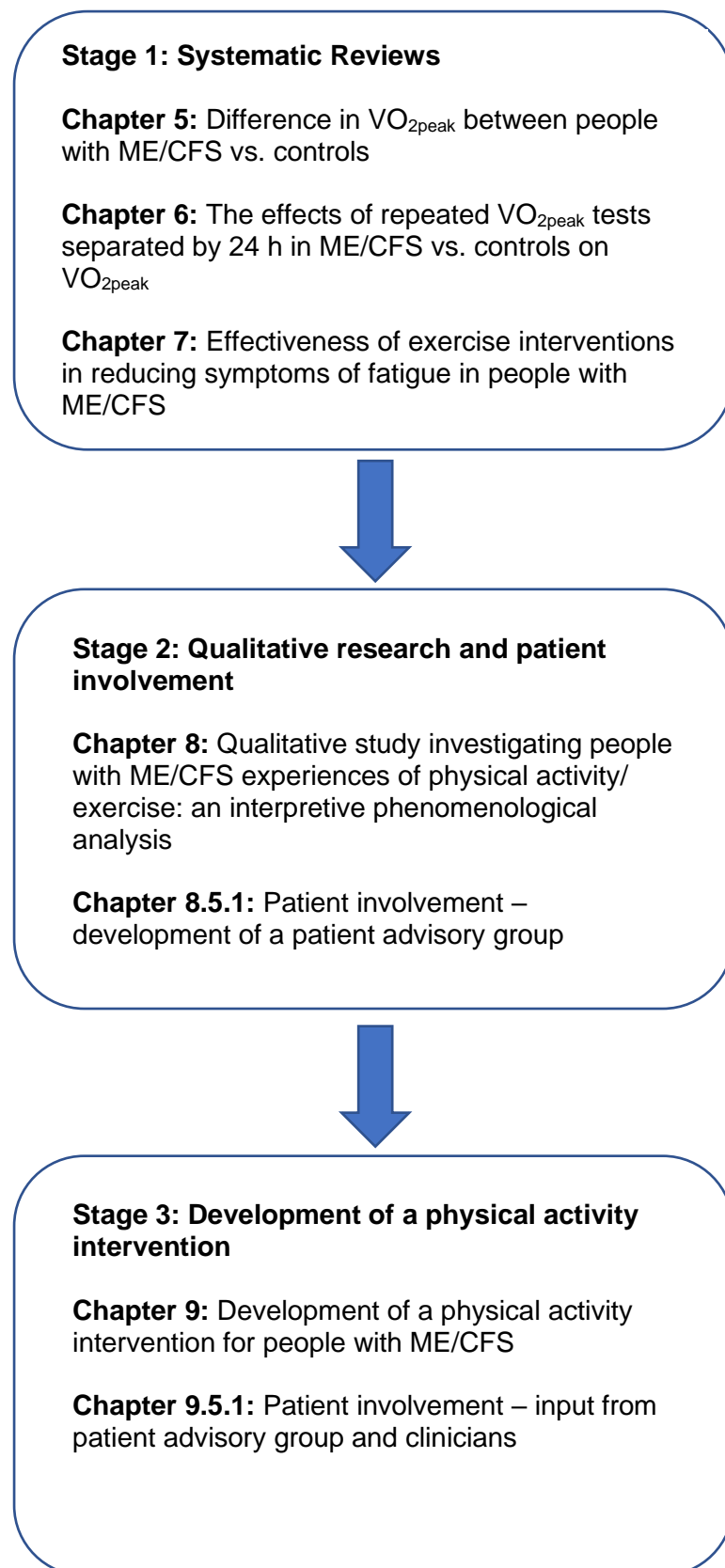
2. *'What user involvement is there going to be? Appropriate 'users' should be involved at all stages.... Qualitative research, as well as providing important insights into processes of change, can be a good way to involve users. It can complement user involvement in steering groups and allows for a wider range of views to be canvassed and systematically incorporated into the design of an evaluation.'* (MRC 2006)

This stage of this thesis (chapter 8) used a qualitative interpretive phenomenological analysis to provide insight into the experiences of people with ME/CFS of physical activity and exercise. A patient/ public involvement (PPI) group was developed alongside this study (Teesside University ME/CFS Patient Advisory Group) to provide insight into this study and future studies.

3. Development of a pilot randomised controlled trial

The final stage of this thesis (chapter 9) then outlined a proposed intervention based on the data generated from the systematic reviews and meta-analyses, along with data generated from the qualitative study. The patient advisory group were asked to provide input into the intervention. Figure 4.1 provides an overview of these three stages and how the chapters relate to each stage.

Figure 4.1; Overview of thesis



Chapter 5: Assessing the extent of the difference in peak oxygen uptake in people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) compared to apparently healthy controls.

5.0 Background

Peak oxygen uptake (VO_{2peak}) is a common measure of cardiovascular-respiratory fitness and has been shown to be a strong predictor of mortality in men (Myers *et al.*, 2002; Khan *et al.*, 2014), women (Aspenes *et al.*, 2011), adults with and without cardiovascular risk factors (Laukkanen *et al.*, 2004; Laukkanen *et al.*, 2016) and patients with coronary heart disease (Keteyian *et al.*, 2008). Reduced physical activity is also associated with a reduction in VO_{2peak} (Aspenes *et al.*, 2011). Furthermore, although the majority of activities of daily living are undertaken at submaximal exercise intensities, VO_{2peak} is thought to be ecologically relevant, subject to evolutionary selection (Garland and Carter, 1994) and sets the upper limit for relatively sustainable energy expenditure.

It has also been shown that people with ME/CFS demonstrate lower levels of physical activity when compared to controls (Evering *et al.*, 2011). Reduced physical activity could lead to a lower VO_{2peak} . To date, research has been equivocal with some studies reporting those with ME/CFS demonstrating a lower VO_{2peak} (Sisto *et al.*, 1996; DeBecker *et al.*, 2000) while other researchers have reported no substantial difference between people with

ME/CFS and healthy controls (Bazelman *et al.*, 2001; Sargent *et al.*, 2002; Cook *et al.*, 2003; Cook *et al.*, 2005).

Only one research group (Nijs *et al.*, 2011) has attempted to synthesise the findings using a systematic review; however, these researchers only provided a description of the findings from these studies and did not attempt a quantitative synthesis. The aim of this study therefore is to provide a meta-analysis of the cross-sectional studies on VO_{2peak} in people with ME/CFS compared to apparently healthy controls.

5.1 Aim of review

The aim of this review is to assess the extent of the difference in VO_{2peak} in people with ME/CFS versus apparently healthy controls.

This review was registered in the PROSPERO register for Systematic Reviews (CRD42014010151)

(http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010151). Three changes were made from the original protocol: (i) a change of title, (ii) the secondary outcomes of interest mentioned in the protocol were not assessed, and (iii) a meta-regression was conducted with study quality as a moderator yet was not reported in the original protocol.

This review was published in the International Journal of Sports Medicine (Franklin *et al.*, 2019) (<https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0802-9175>).

5.2 Design

This study was a systematic review and meta-analysis. A systematic review is a literature review with clear and explicit stages, with the aim of limiting bias to allow the development of scientifically robust conclusions (Boland *et al.*, 2017). This process involved identifying all available literature on a topic through a comprehensive search strategy. The selection of studies was based on clear inclusion and exclusion criteria followed by a critical appraisal of the included studies. Finally, the study findings are synthesised to allow the formulation of evidence-based conclusions (Boland *et al.*, 2017). Unlike narrative reviews, these clear and explicit stages should aid in reducing bias, as the authors are not only selecting papers that support their own beliefs of a topic (Bettany Saltikov, 2010). However, the findings from a systematic review are limited by the quality of the included studies. Moher *et al.* (2010) further argued that the reporting of systematic reviews is still 'not optimum'. Further still, systematic reviews often do not include important and explicit scientific criteria such as assessing study quality and assessing for publication bias (or small study effects) (Moher *et al.*, 2010). To aid with this the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Liberati *et al.*, 2009) were used in the reporting of this review.

5.3 Criteria for selecting studies

McKenzie *et al.* (2019) stated that one of the unique aspects of a systematic review is that the inclusion and exclusion criteria are specified in advance before the literature search or study selection process has taken place. This is to maintain the transparency and rigour of the review and to reduce bias by

preventing authors from only selecting studies that agree with their own view (Bettany-Saltikov and McSherry, 2016). These should be related to the research question and developed with the method of synthesis in mind (McKenzie *et al.*, 2019). The use of acronyms such as PICO/PIO and PEO have been shown to be effective ways in summarising this information (McKenzie *et al.*, 2019). For the purposes of this review the inclusion and exclusion criteria were described using the terms; exposure (ME/CFS), outcome (VO_{2peak}) and types of studies (observational).

The eligibility criteria for this review were:

Exposure. Comparative studies were included involving adults (over 18 years old) with any clinical diagnosis of ME/CFS using any recognised diagnostic definition. The specific diagnostic definitions for this study included Holmes *et al.* (1988), the Oxford Criteria (Sharpe *et al.*, 1991), Schluederberg *et al.* (1992), Fukuda *et al.* (1994), Komaroff *et al.* (1996), the Canadian Criteria (Carruthers *et al.*, 2003), NICE, (2007) and the International Consensus Criteria (ICC) (Carruthers *et al.*, 2011). To be included studies were required to compare people with ME/CFS with apparently healthy control participants.

Outcome. Any study that assessed VO_{2max} or VO_{2peak} as a maximal test was included. Studies that included multiple VO_{2peak} tests were included; however, only data from the first test was used. Studies that included any pre-examination, such as any cognitive tests conducted before the peak exercise test, were also included. Studies must have collected data on expired air to

be included and studies were excluded if a predicted VO_{2peak} was calculated from other variables or from a submaximal test.

Types of study. Any cross-sectional observational study was included. Studies were required to be published in a peer-reviewed journal, with a description of the data collection methods.

5.4 Search strategy

A Chartered Information Professional conducted a systematic search from inception up to March 2018 of Cochrane, PubMed, PsycINFO, Web of Knowledge, Embase, Scopus and Medline using the following search terms and strategy (involving Boolean operators):

“chronic fatigue syndrom*”

AND

(“peak” OR “maxim*” OR “max”)

AND

(“oxygen uptake” OR “oxygen consumption” OR “aerobic power” OR “aerobic fitness” OR “cardiorespiratory fitness” OR “cardio?respiratory fitness” or “VO₂peak” or “VO₂max” or “VO₂?peak” or “VO₂?max” or “cardiorespiratory function” or “cardio?respiratory function” or “exercise capacit*” or “physical fitness” or “functional capacit*” or “exercise performance*”).

Reference lists of papers were checked. Grey literature was not included, as this has not been peer-reviewed and a full assessment of the methodological

quality could not be made. Only English language databases were searched, and only papers written in English were considered for this review.

5.5 Selection of studies

Information relating to study selection was collated in Microsoft Excel. Two reviewers independently assessed all titles and abstracts. JF assessed all papers for first selection, a second reviewer assessed the first half of the titles and abstracts, and a third reviewer assessed the second half. Where disagreements arose, discussion took place with three reviewers involved with the selection process. Studies were included in the second selection when they clearly met the inclusion criteria based on title and abstract or where the information was not clear. Articles that clearly did not meet the inclusion criteria were excluded.

For studies that were included in the second selection, full texts were obtained and all papers were assessed by JF. Two reviewers assessed a sample of studies and discussion took place between the three reviewers about the suitability of the remaining papers. A consensus was then reached on the papers that were then included.

5.6 Assessment of methodological quality

A modified version of the Systematic Appraisal of Quality for Observational Research (SAQOR) (Ross *et al.*, 2011) was used to assess the methodological quality of the included studies. The framework was modified for the specific nature of this study. This involved removing question 1 of the

framework as it was decided that it was difficult to comment on the representativeness of the heterogeneous ME/CFS population. Questions on follow-up were removed from the assessment and information about fatigue following a maximal test was not analysed. The potential confounding influences for this review were identified as 1) the use of and reporting of criteria used to achieve maximum effort, 2) any methods used to standardise equipment used in the maximal test, such as calibration of equipment and habituation. 3) Any other confounding variables such as controlling for caffeine intake and physical activity in the previous 48 hours.

A numerical score was also provided for each study with each question on the framework being awarded a '0' if the criterion was not met in the study, a '1' if the study had made an attempt, and a '2' if the criterion was met. For example, if a study stated that criteria were used to assess if a genuine maximum effort was achieved, this would result in a score of one. If a study used criteria and reported these, it would receive a score of two. Each paper could achieve a maximum score of 32 on the modified scale. The modifications of the assessment tool were made after discussion within the research team and agreement on the key information to consider within the papers. Assessment of methodological quality was conducted by JF; however, discussions took place within the research team on a sample of studies. Further discussions also took place with regards to the key design aspects of the studies, with particular focus on the exposure and outcome in each paper, along with any concerns or queries, which may have become apparent during the quality

assessment. The quality assessment for each paper was conducted twice and the scores of each paper checked for consistency.

5.7 Data Extraction

Data was extracted from each of the included papers into a Microsoft Excel spreadsheet. Extracted data included sample size; the criteria used for the diagnosis of ME/CFS, mean age, length of illness, and ME/CFS severity score. The outcome was VO_{2peak} and, although some studies may have referred to this as VO_{2max} , for the purposes of this review the term VO_{2peak} will be used when discussing the results of all studies. It was recorded and coded whether the study included any methods to assess maximum effort, plus the score for each study for overall quality. When data were not presented in the format needed, or the relevant data was not provided, the authors were contacted for the original data (table 5.1). Where the standard error was reported, the standard deviation was calculated ($SD = SE \times \sqrt{N}$). When a study provided a confidence interval of the mean difference, but with no standard deviations, the confidence interval was entered directly in the software data sheet. When data was reported solely in a figure, the Digitizelt computer programme (Digitizelt, 2017) was used to extract data pertaining to VO_{2peak} .

Table 5.1; Researchers contacted during data extraction

Study Researcher (Email)	Information requested	Response
Bazelman <i>et al.</i> (2001) Dr E. Bazelmans (Ellen.Bazelmans@radboudumc.nl)	VO _{2peak} reported as l.min ⁻¹ , data as ml.kg ⁻¹ min ⁻¹ was requested	Original data set was provided and results for ME/CFS and controls were calculated
Jones <i>et al.</i> (2012) Professor Julia Newton (j.l.newton@ncl.ac.uk)	Data is provided in figures, numerical data requested	No response

5.8 Data analysis

Group means and standard deviations for VO_{2peak} were inputted into Comprehensive Meta-Analysis Software version 3 (CMA) in duplicate for data analysis. A random effects meta-analysis was conducted. For any study that stratified results by sex, the male and female samples were combined to derive a single effect. Combined means and standard deviations for Sargent *et al.*, (2002) and Vermeulen and Vermeulen van Eck (2014) were calculated using the method described by Higgins and Green (2011). The DerSimonian and Laird (method of moments) estimator with z-distribution was conducted to assess heterogeneity. Egger's regression coefficient and its uncertainty (confidence interval) were used to explore small-study effects. In the event of substantial heterogeneity (between-study variation in effect size), the rating of study quality (0-32 scale) was explored as a putative moderator.

A random effects meta-analysis, unlike a fixed effects meta-analysis, does not assume that there is a single true effect and instead estimates the mean of a distribution of effects (Borenstein *et al.*, 2009). This is in contrast to a fixed-

effect meta-analysis were it is assumed that the true effect size for all studies is identical and therefore the information in smaller studies can be to some extent 'ignored' as there is more accurate information in the larger studies (Borenstein *et al.*, 2009). However, in a random effects meta-analysis, since each study provides information about a different effect size, a random effects meta-analysis ensures all effect sizes are represented, even if imprecise, as the study has information about an effect that no other has (Borenstein *et al.*, 2009). In a random effects meta-analysis the 95% confidence interval (95%CI) provides an estimation of confidence, or the error of estimation of the mean. However, to calculate the distribution of true effect sizes, the 95% prediction interval (95%PI) which incorporates true dispersion and error, needs to be calculated (Borenstein *et al.*, 2009). As the 95%CI for a random effects meta-analysis quantifies the accuracy of the mean, however does not provide a distribution of true effect sizes (Borenstein *et al.*, 2009). Therefore, to make inferences the 95%PI was derived, providing a plausible range for the expected effect (difference between ME/CFS and control) in a future study conducted in similar settings (IntHout *et al.*, 2016). Using this approach, we also calculated the probability that the effect in a future study would be clinically relevant. Schunemann *et al.* (2005) defined a minimal important difference as:

'The smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management.'

Although different terminology is used when describing a minimal important difference including, minimally importance change (MIC) (Takeshima *et al.*, 2014), minimal important difference (MID) (Johnston *et al.*, 2010) and minimal clinically important difference (MCID). For the purpose of this thesis the term will MCID will be used throughout. The threshold for MCID was derived using an anchor-based approach from recent epidemiological data. Anchor-based methods rely on examining the associations between the outcomes under investigation and an anchor; an independent measure that clinicians can easily interpret (Schunemann *et al.*, 2005).

To calculate the MCID, data from Laukanen *et al.*, (2016) which reported that a $1 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ increment in $\text{VO}_{2\text{peak}}$ was associated with a 9% relative risk reduction for all-cause mortality (hazard ratio 0.91) was used. The smallest worthwhile relative risk reduction in mortality was defined as a hazard ratio of 0.9 (Hopkins *et al.*, 2009), implying that for every 10 deaths, one would be prevented with the associated increase in $\text{VO}_{2\text{peak}}$. Using the data from the Laukanen *et al.*, (2016) study, the MCID is defined in this review as $1.1 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ – a small effect. The thresholds for moderate and large effects are 3.8 and $7.3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, respectively, equivalent to hazard ratios of 0.7 and 0.5 (Hopkins *et al.*, 2009).

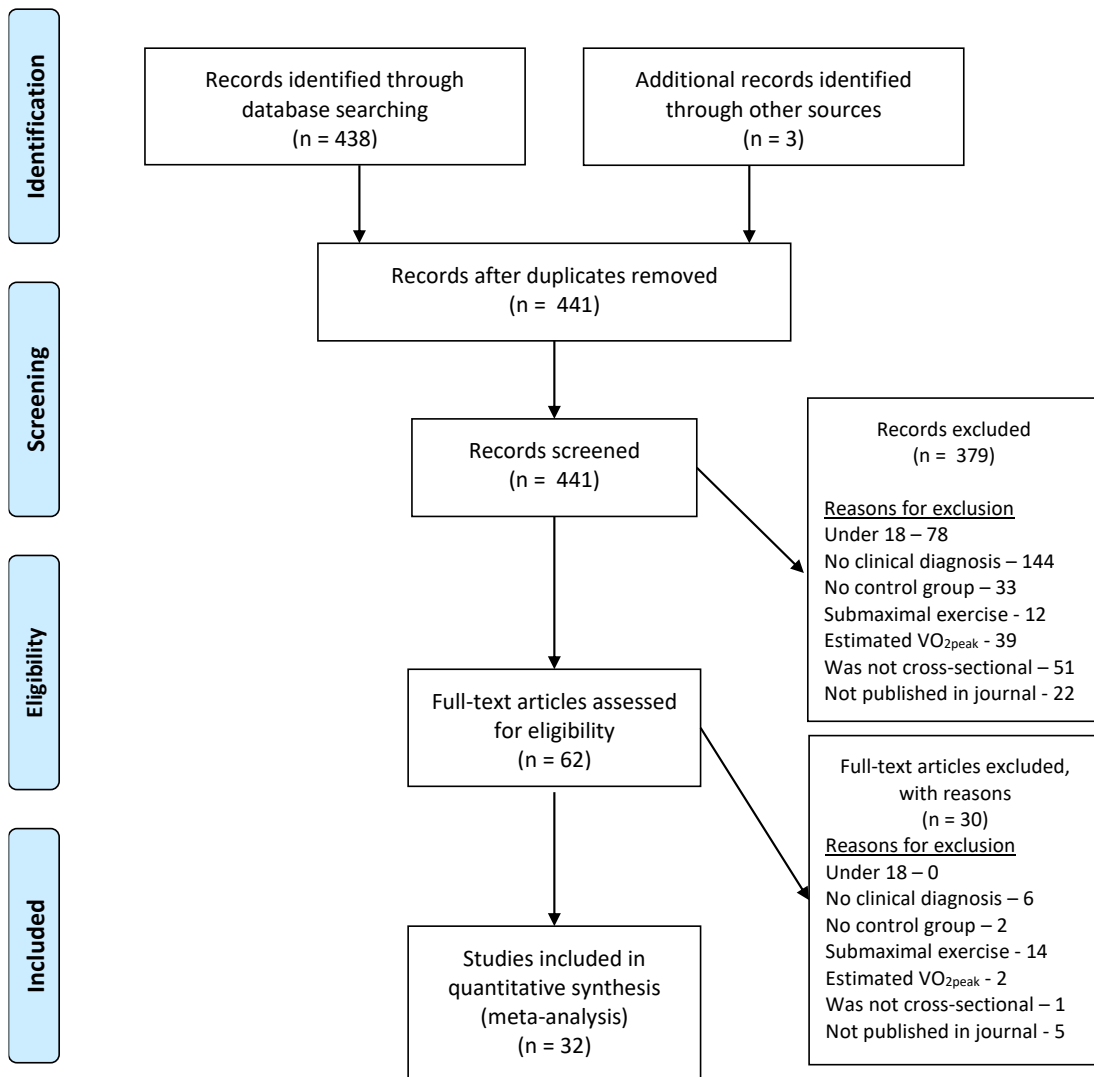
5.9 Results

5.9.1 Results of Literature Search, 1st and 2nd Selection

Figure 1 provides an overview of the search results and the results of the selections. Searching electronic databases yielded 438 papers. A further 3 papers were found from checking reference lists resulting in a combined total of 441 papers that were assessed for eligibility in to the review.

Following the first selection of studies the percentage agreement between JF and reviewer two was 60%; JF identified 25 papers to be assessed in the second selection and reviewer two identified 15 papers. The percentage agreement for first selection between JF and reviewer three was 100% with both reviewers identifying 59 papers to be assessed in the second selection. A further 11 studies were deemed by one of the three reviewers as 'maybe'. A discussion between the three reviewers then took place and they assessed the 95 title and abstracts identified in detail to reach a consensus on which studies to progress. It was decided that 62 papers were to be included in the second selection process. The main reasons for the discrepancy between the reviewers was due to lack of clarity in the abstract around the comparison group, the use of adolescents instead of adults, and predicted $\text{VO}_{2\text{peak}}$ from heart rate and workload as opposed to measured O_2 consumption from expired air. The second selection of studies resulted in the exclusion of 30 papers and subsequently 32 papers were included in the meta-analysis.

Figure 5.1; PRISMA diagram summarising study selection



5.9.2 Overview of Included Studies

Key characteristics of the included papers can be seen in Tables 1 and 2. All studies included in this review included a group of cases with ME/CFS and a comparison group of apparently healthy participants. The comparison group were defined as controls or healthy sedentary controls. A total of 23 of the included papers made an attempt to match participants on some characteristics, while the remaining 9 papers provided information on any

statistically significant difference between the two groups. However, these authors did not match for characteristics at the start of the study. Twenty-four papers cited Fukuda *et al.* (1994) as the diagnostic criteria for ME/CFS. The mode of exercise test in 23 studies was cycle ergometry, with a treadmill test utilised in the remaining 9 papers. All papers collected expired air during the exercise test to calculate VO_{2peak} .

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Table 5.2; Summary of Study Characteristics relating to comparing patients and controls.

Study	ME/CFS diagnostic definition	ME/CFS sample size	Control sample size	Controls defined in study as	ME/CFS and controls matched for	Mode of exercise
Jammes <i>et al.</i> (2012)	Fukuda	43	23	Healthy Caucasian volunteers	Sex, age, weight, socio-economic status	Cycle ergometer
Jones <i>et al.</i> (2012)	Fukuda	18	12	Sedentary normal controls	Age, sex, BMI	Cycle ergometer
Robinson <i>et al.</i> (2010)	Fukuda	6	6	Healthy controls	Age, sex, BMI	Cycle ergometer
Jammes <i>et al.</i> (2009)	Fukuda	9	9	Controls, healthy volunteers	Sex, age, weight	Cycle ergometer
Cook <i>et al.</i> (2006)	Fukuda	29	32	Sedentary Healthy controls	-	Cycle ergometer
Jammes <i>et al.</i> (2005)	Fukuda ⁺	15	11	Healthy Sedentary Volunteers	Sex, age, weight	Cycle ergometer
LaManca <i>et al.</i> (2001)	Holmes	19	20	Healthy Sedentary normotensive	Age, sex, race, education	Graded walking test
Bazelmans <i>et al.</i> (2001)	Fukuda	20	20	Matched neighbourhood controls	Age, sex	Bicycle ergometer
DeBecker <i>et al.</i> (2000)	Fukuda or Holmes	157	163	Age-matched sedentary women	Age, sex	Bicycle ergometer
Fulcher and White (2000)	Sharpe	66	30	Healthy sedentary controls	-	Treadmill walking test
LaManca <i>et al.</i> (1999)	Schluederberg or Holmes or Fukuda	20	14	Sedentary healthy control females	Sex, age, education	Treadmill exercise test
Togo <i>et al.</i> (2010)	Fukuda	17	16	Healthy female controls	Sex	Cycle ergometer
Cook <i>et al.</i> (2003b)	Fukuda	15	19	Healthy controls	-	Cycle ergometer
Cook <i>et al.</i> (2003a)	Fukuda or Holmes	19	20	Sedentary healthy controls	Sex, age	Treadmill test
Sargent <i>et al.</i> * (2002)	Fukuda	16	16	Sedentary controls	Sex, age, mass, height	Cycle ergometer

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Sargent <i>et al.</i> * (2002)	Fukuda	17	17	Sedentary controls	Sex, age, mass, height	Cycle ergometer
Inbar <i>et al.</i> (2001)	Holmes	15	15	Healthy sedentary	Age, sex	Treadmill (modified Balke protocol)
Vermeulen <i>et al.</i> (2010)	Fukuda	15	15	Health sedentary controls	-	Cycle ergometer
VanNess <i>et al.</i> (2007)	Fukuda	6	6	Sedentary female controls	-	Treadmill (modified Bruce protocol) or cycle ergometer
Georgiades <i>et al.</i> (2003)	Fukuda	12	11	Sedentary controls	Age, sex, anthropometric characteristics, habitual physical activity status	Cycle ergometer
Farquhar <i>et al.</i> (2002)	Fukuda	17	17	Healthy controls	-	Upright cycle
Rowbottom <i>et al.</i> (1998)	Holmes and Komaroff	16	16	Healthy controls	Age, sex	Treadmill (modified Bruce protocol)
Sisto <i>et al.</i> (1996)	Holmes	10	17	Sedentary healthy controls	Sex, age, education	Treadmill protocol
Suarez <i>et al.</i> (2010)	Fukuda	44	25	Sedentary controls	-	Cycle ergometer
Claypoole <i>et al.</i> (2001)	Fukuda	21	21	Healthy twin	Monozygotic twin	Cycle ergometer
Snell <i>et al.</i> (2013)	Fukuda	51	10	Sedentary controls	Age, BMI	Cycle ergometer
Riley <i>et al.</i> (1990)	Holmes	13	13	Healthy subjects	-	Treadmill (Bruce protocol)
Fischler <i>et al.</i> (1997)	Sharpe and Fukuda	10	11	Healthy controls	Sex, age, weight	Cycle ergometer
Aerenhouts <i>et al.</i> (2015)	Fukuda	42	24	Healthy Inactive relative, friend or acquaintance	Sex, age	Cycle ergometer

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Ickmans <i>et al.</i> (2013)	Fukuda	30	13	Healthy Inactive relative, friend or acquaintance	Sex, age, height, body mass, BMI	Cycle ergometer
Vermeulen and Vermeulen van Eck (2014) (Male)*	Fukuda	25	7	Sedentary men	-	Cycle ergometer
Vermeulen and Vermeulen van Eck (2014) (Female)*	Fukuda	178	11	Sedentary women	-	Cycle ergometer
Hodges <i>et al.</i> (2017)	Fukuda and Carruthers and ICC	10	10	Healthy controls	Sex, age	Cycle ergometer
Moneghetti <i>et al.</i> (2018)	Fukuda and ICC	24	24	Sedentary controls	Age, sex, race	Upright ergocycle

- Study did not match for any characteristics (however the study may have provided information on key characteristics in each group)

* Information presented in table by sex however data was combined in meta-analysis

+ This paper referenced Fukuda et al [15] in the introduction and made reference to this in the methods but this was not explicitly referenced in the methods.

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Table 5.3; Summary of intervention and results from included papers

Study	Description of intervention	Results of study VO _{2peak} (ml.kg ⁻¹ /min ⁻¹) Mean ± SD P-values and 95%CI reported if reported in paper
Jammes <i>et al.</i> (2012)	Cycle ergometer, initially 2-min, 0 W. Then increased 20 W/ min ⁻¹ . Criteria for max, plateau in VO ₂ , reaching predicted maximum values for VO ₂ , reaching predicted max HR, RER > 1.1.	CFS VO _{2peak} 27.5 ± 8.2 Control VO _{2peak} 26.7 ± 5.28
Jones <i>et al.</i> (2012)	Participants cycled on a cycle ergometer between 60 & 90 rpm. Initial resistance 40 W, increased 10 W/ min.	CFS VO _{2peak} 20.9 ± 5.8 Control VO _{2peak} 27.1 ± 6.2
Robinson <i>et al.</i> (2010)	Cycled on a cycle ergometer at 70 rpm. Initial workload was 65 W and this was increased by 15W/ 2 min. VO _{2max} was VO ₂ averaged over the highest 30s. Criteria for max required to meet 3 of the following. Change in VO ₂ < 2ml.kg ⁻¹ /min ⁻¹ between last minute of final and previous workloads. RER ≥ 1.15, reaching age predicted max HR, blood lactate > 8mmol/ L.	CFS VO _{2peak} 27.8 ± 3.7 Control VO _{2peak} 32.1 ± 8.3 P = 0.287
Jammes <i>et al.</i> (2009)	Cycle ergometer, initially 2 min, 0 W. Then increased 20 W/ min. Criteria for max, plateau in VO ₂ , reaching predicted max HR, RER > 1.1.	CFS VO _{2peak} 33 ± 12 Control VO _{2peak} 30 ± 9
Cook <i>et al.</i> (2006)	Cycle ergometer. 3-minute warm up at 20 W maintaining between 60 and 70 rpm. Workload increased by 5 W/ 20secs. Criteria for max, required to meet 2 of the following. RER ≥ 1.1, achieving 85% of age predicted max. RPE ≥ 17, change in VO ₂ < 200ml with an increase in work.	CFS VO _{2peak} 25.7 ± 6 Control VO _{2peak} 29.7 ± 8
Jammes <i>et al.</i> (2005)	2 min rest period followed by 2-min 0 W workload. Beginning at 20 W, workload increased by 20 W/ min.	CFS VO _{2peak} 24 ± 3.9 Control VO _{2peak} 37 ± 9.9 P < 0.01
LaManca <i>et al.</i> (2001)	Graded walking test to exhaustion	CFS VO _{2peak} 27.7 ± 6.97

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		Control VO _{2peak} 30.4 ± 4.47 P > 0.10
Bazelmans <i>et al.</i> (2001)	Cycle ergometer. Workload was increased each minute by 10% of estimated workload. The steps varied from 10-30 W/ min. Criteria for max required to meet one of the following. Attained predicted max HR, lactate production > 10mmol/ min, increase CO ₂ pressure in blood at maximal workload compared to rest.	CFS VO _{2peak} 27.77 ± 7.17 Control VO _{2peak} 29.88 ± 7.95
DeBecker <i>et al.</i> (2000)	Cycle ergometer. CFS patients started at 10 W and workload was increased 10 W/min. Control group started at 40 W and workload was increased 35 W/ 3mins. Criteria for max, required to meet two criteria RQ > 1 and reaching 85% of age predicted max HR.	CFS VO _{2peak} 22.7 ± 5.01 Control VO _{2peak} 32.9 ± 7.66 P < 0.001
Fulcher and White (2000)	Walking test. Constant speed of 5kph. Gradient increased by 2.5%/ 2mins.	CFS VO _{2peak} 30.6 ± 8.2 Control VO _{2peak} 34.1 ± 6.8 P = 0.05
LaManca <i>et al.</i> (1999)	Treadmill exercise test. 4 mins seated rest. Test started at 2.5mph and no incline. Each test stage lasted 3 minutes. This first increase in workload involves increasing the speed to 3.5mph. For each subsequent stage the incline was increased by 2%.	CFS VO _{2peak} 28.6 ± 6.7 Control VO _{2peak} 30.4 ± 4.2
Togo <i>et al.</i> (2010)	Cycle ergometer. 3 mins unloaded warm-up. Test began at 20 W, workload then increased by 5 W/ 20secs. Participants had to maintain 60rpm. Criteria for max, required to meet one of the following, 80% age predicted max HR, RER ≥ 1.1.	CFS VO _{2peak} 20.1 ± 5.4 Control VO _{2peak} 24.5 ± 5.1
Cook <i>et al.</i> (2003b)	Cycle ergometer. 3 minutes unloaded pedalling maintaining 60rpm. Workload increased by 30 W/ min. Criteria for max, participants had to meet at least two of the following; RER ≥ 1.1, achieved 85% age predicted max HR, plateau or decline of VO ₂ despite increasing workload.	CFS VO _{2peak} 29 ± 6.7 Control VO _{2peak} 30.8 ± 7.1

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Cook <i>et al.</i> (2003a)	Motorised treadmill. Began with 4 minutes seated rest. Each exercise stage lasted 3 minutes. For the initial stage the treadmill was at 67m/min, no incline. For the second stage this was increased to 94m/min. For the remaining stages, treadmill speed was not increased but the incline increased by 2% for each stage. Criteria for max, participants had to meet at least two of the following; RER ≥ 1.1 , achieved 90% age predicted max HR, plateau or decline of VO_2 despite increasing workload.	CFS $\text{VO}_{2\text{peak}}$ 29.8 ± 5.8 Control $\text{VO}_{2\text{peak}}$ 30.7 ± 4.6
Sargent <i>et al.</i> (2002)*	Cycle ergometer. 10 mins rest period followed by 2 mins unloaded cycling at 50rpm. Following this workload was increased by 25 W/ 2mins. Criteria for max, participants were required to fulfil at least two of the following; achieve age predicted max HR ± 11 bpm. RER ≥ 1.1 , blood lactate ≥ 8 mmol.	Male CFS $\text{VO}_{2\text{peak}}$ 40.5 ± 6.7 Control $\text{VO}_{2\text{peak}}$ 43.3 ± 8.6 Female CFS $\text{VO}_{2\text{peak}}$ 30.0 ± 4.7 Control $\text{VO}_{2\text{peak}}$ 34.2 ± 5.6 P = 0.002 (for female only)
Inbar <i>et al.</i> (2001)	CPET on treadmill (modified Balke protocol). Speed constant (2.0-3.5mph) slope elevated by 2%/ min. Criteria for max, VCO_2 increased relative to increase in VO_2 . V_E/VO_2 versus VO_2 curve begins to rise as V_E/VCO_2 versus VO_2 curve remains constant or decreases, gas exchange ratio changes to a steeper curve.	CFS $\text{VO}_{2\text{peak}}$ 19.8 ± 5.3 Control $\text{VO}_{2\text{peak}}$ 27.3 ± 5.6 P = 0.001
Vermeulen <i>et al.</i> (2010)	CPET on cycle ergometer. 3 mins no activity, 3 mins unloaded pedalling. Followed by pedalling against increasing resistance.	CFS $\text{VO}_{2\text{peak}}$ 22.3 ± 5.7 Control $\text{VO}_{2\text{peak}}$ 31.2 ± 7.0 P < 0.01
VanNess <i>et al.</i> (2007)	CFS patients participated in a Modified Bruce treadmill test or 10 W/ min ramping protocol on a cycle ergometer. Controls participated in a 20 W/min ramping protocol.	CFS $\text{VO}_{2\text{peak}}$ 26.23 ± 4.92 Control $\text{VO}_{2\text{peak}}$ 28.43 ± 7.27 NS
Georgiades <i>et al.</i> (2003)	Cycle ergometer. Workload increase varied between 3 and 10 W/ min.	CFS $\text{VO}_{2\text{peak}}$ 21.2 ± 6.3 Control $\text{VO}_{2\text{peak}}$ 28.3 ± 6.4

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Farquhar <i>et al.</i> (2002)	Monark upright Cycle. 2 min stages workload increased by 25- 30 W/ stage.	CFS VO _{2peak} 22.0 ± 4.95 Control VO _{2peak} 33.6 ± 7.83 P < 0.001
Rowbottom <i>et al.</i> (1998)	Modified Bruce treadmill protocol. Test started with a 3min stage at 3 kph, 1% gradient. Speed was increased by 1kph/ 3mins until a speed of 6 kph was reached. Workload was then increased by increasing the gradient by 2%/ 3mins.	CFS VO _{2peak} 34.7 ± 12 Control VO _{2peak} 36.2 ± 9.2 P > 0.05
Sisto <i>et al.</i> (1996)	Treadmill protocol. Six discontinuous 4-min exercise stages with no incline (1mph, 2mph, rest, 1.5mph, 2.5mph, rest, 3mph, 3.5mph). at 3.5mph incline was increased by 2%/ min. Criteria for max, had to meet two of the following; RER > 1.0, achieve age predicted max HR, plateau or decline in VO ₂ at final workload.	CFS VO _{2peak} 28.1 ± 5.1 Control VO _{2peak} 32.1 ± 4.3 P = 0.05
Suarez <i>et al.</i> (2010)	Cycle ergometer. Started at 0 W for 4 mins. Workload increased by 20 W/ min.	CFS VO _{2peak} 17.1 ± 5.5 Control VO _{2peak} 25.6 ± 6.0 P < 0.001
Claypoole <i>et al.</i> (2001)	Cycling ergometer. Unloaded pedalling for 4 mins. Workload increased by 20 W/ min.	CFS VO _{2peak} 18.9 ± 4.8 Control VO _{2peak} 20.5 ± 4.4 P = 0.056
Snell <i>et al.</i> (2013)	3 mins rest followed by 1 min unloaded cycling, participants asked to maintain 60 to 80 rpm. Workload increased by 5 W/ 20secs (15 W/ min). Criteria for max, participants required to achieve an RER ≥ 1.1 and at least one of the following; plateau in oxygen consumption, RPE > 17, achieve 85% age predicted max HR.	CFS VO _{2peak} 21.51 ± 4.09 (95%CI 20.34 to 22.71) Control VO _{2peak} 25.04 ± 4.41 (95% CI 22.35 to 27.73) NS
Riley <i>et al.</i> (1990)	Bruce treadmill protocol. Modified to include an initial stage with a 5% gradient.	CFS VO _{2peak} 31.8 ± 5.3 Control VO _{2peak} 37.9 ± 5.1 P < 0.05

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Fischler <i>et al.</i> (1997)	Cycle ergometer. Men; started at 50W workload increased by 50 W/ 3 mins. Women; started at 30W workload increased by 40W/ 3mins.	CFS VO _{2peak} 25.2 (no SD presented) Control VO _{2peak} 36.6 (no SD presented) P = 0.001 Mean difference 11.4 (95%CI 5.1 to 17.8)
Aerenhouts <i>et al.</i> (2015)	Cycle ergometer. Test started at 60 W, workload increased by 30 W/ min. Participants required to maintain 60-70rpm.	CFS VO _{2peak} 19.5 ± 4.7 Control VO _{2peak} 29.9 ± 5.5 P < 0.001
Ickmans <i>et al.</i> (2013)	Cycle ergometer. Test started at 60 W, workload increased by 30 W/ min. Participants required to maintain 60-70rpm.	CFS VO _{2peak} 19.1 ± 4.6 Control VO _{2peak} 27.2 ± 5.6 P < 0.001
Vermeulen and Vermeulen van Eck (2014)*	CPET on cycle ergometer. 3 mins without activity, 3 mins unloaded pedalling, resistance increased until exhaustion.	Male CFS VO _{2peak} 24 ± 7.2 Control VO _{2peak} 27.3 ± 3.7 Female CFS VO _{2peak} 20.3 ± 5.0 Control VO _{2peak} 27.4 ± 7.2
Hodges <i>et al.</i> (2017)	Cycles at between 50 and 80 rpm. Starting at 15W, intensity increased by 15W/ min. Test terminated at voluntary exhaustion or couldn't maintain 50 rpm. ACSM (2014) criteria used.	CFS VO _{2peak} 24.95 ± 8.9 Control VO _{2peak} 31.99 ± 10.88
Moneghetti <i>et al.</i> (2018)	One day ramp protocol with increments of 15 to 25W / 90 secs	CFS VO _{2peak} 28.6 ± 6.7 Control VO _{2peak} 29.7 ± 8.3 P=0.23

Papers are presented in the order in which they were returned during the literature search.

*Results presented in study by sex however these were combined in the meta-analysis and meta-regression

(Abbreviations; CPET cardiopulmonary exercise test. HR heart rate. W Watt. Min minutes. RER respiratory exchange ratio. kph kilometres per hour. mph miles per hour. NS non-significant. ACSM American College of Sports Medicine)

5.9.3 Assessment of Methodological Quality

Table 3 provides an overview of the assessment of methodological quality. All studies included within this review used recognised criteria for the diagnosis of ME/CFS. Fourteen papers provided a good overview of the source of the ME/CFS sample, 2 papers described the sampling method that was used, and 4 papers provided a sample size calculation. All studies included a control group and this group was easily distinguishable from the ME/CFS group in all studies. 12 papers provided a good summary of the source of the control group. In all studies comparisons between groups were made on key variables; however, not all papers matched for these characteristics at the start of the study.

The information pertaining to the exposure (ME/CFS vs. controls) and outcome (measurement of VO_{2peak}) was good in 31 and 25 of the papers, respectively. The key confounding variables that were controlled for varied across the studies and there were no key variables that were consistently measured. 9 papers provided information about the criteria used to assess maximum effort and reported this information. A further 7 papers reported using criteria to assess maximum effort however this information was not presented in the study. 16 papers provided no information about how maximum effort was assessed.

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Table 5.4, Summary of the Assessment of Methodological Quality.

Study	Source of the sample	Sampling method	Sample size (Power)	Inclusion and exclusion	Control group included	Control group easily identifiable	Source of the controls	Controls are matched or randomised	Statistical difference calculated	Assessment of exposure	Assessment of outcomes	Exercise test described adequately	Criteria for achieving max	Any other confounders	Missing data	Accurate presentation of results	Total score
Jammes <i>et al.</i> (2012)	-	-	-	*	**	**	-	**	-	**	**	**	*	-	-	*	15
Jones <i>et al.</i> (2012)	**	-	-	**	**	**	-	**	**	**	**	**	-	**	-	*	21
Robinson <i>et al.</i> (2010)	-	-	-	*	**	**	-	**	**	**	**	**	**	-	-	**	19
Jammes <i>et al.</i> (2009)	-	-	-	*	**	**	-	**	-	**	**	**	*	-	-	*	15
Cook <i>et al.</i> (2006)	**	**	-	**	**	**	**	**	**	**	**	**	**	**	-	**	28
Jammes <i>et al.</i> (2005)	-	-	-	**	**	**	-	**	-	*	**	**	-	-	-	*	14
LaManca <i>et al.</i> (2001)	**	-	-	**	**	**	**	**	**	**	**	-	-	**	-	**	22
Bazelmans <i>et al.</i> (2001)	**	-	-	*	**	**	**	*	**	**	*	*	**	-	-	**	20
DeBecker <i>et al.</i> (2000)	-	-	-	*	**	**	*	**	*	**	**	*	**	-	-	**	18

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Fulcher and White (2000)	**	-	-	**	**	**	**	-	**	**	*	*	-	*	-	**	19
LaManca <i>et al.</i> (1999)	**	-	-	**	**	**	*	**	**	**	**	**	**	*	**	**	26
Togo <i>et al.</i> (2010)	*	*	-	**	**	**	*	**	-	**	**	**	**	-	-	**	21
Cook <i>et al.</i> (2003b)	*	-	**	*	**	**	*	-	**	**	**	**	*	**	**	**	24
Cook <i>et al.</i> (2003a)	**	-	**	**	**	**	**	**	**	**	**	**	*	**	*	**	28
Sargent <i>et al.</i> (2002)*	-	-	**	**	**	**	*	**	*	**	**	**	**	**	-	**	24
Inbar <i>et al.</i> (2001)	**	-	-	**	**	**	**	**	**	**	**	*	*	**	-	**	24
Vermeulen <i>et al.</i> (2010)	**	-	-	**	**	**	-	-	**	**	*	*	-	-	-	**	16
VanNess <i>et al.</i> (2007)	*	-	-	**	**	**	-	-	-	**	*	*	-	**	-	**	15
Georgiades <i>et al.</i> (2003)	-	-	-	*	**	**	-	**	-	**	**	*	-	*	-	**	15
Farquhar <i>et al.</i> (2002)	-	-	-	*	**	**	-	-	**	**	**	*	**	-	-	**	16
Rowbottom <i>et al.</i> (1998)	-	-	-	**	**	**	**	**	-	**	**	**	-	-	-	**	18

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Sisto <i>et al.</i> (1996)	**	-	-	**	**	**	**	**	**	**	**	**	**	*	-	**	25
Suarez <i>et al.</i> (2010)	-	*	-	*	**	**	-	-	-	**	**	**	-	*	-	**	15
Claypoole <i>et al.</i> (2001)	**	**	-	**	**	**	**	**	**	**	*	*	-	**	-	**	24
Snell <i>et al.</i> (2013)	-	*	-	**	**	**	-	**	**	**	**	**	*	-	-	**	20
Riley <i>et al.</i> (1990)	-	*	-	**	**	**	*	-	-	**	**	*	-	-	-	**	15
Fischler <i>et al.</i> (1997)	**	*	-	**	**	**	*	**	**	**	**	*	-	**	-	*	20
Aerenhouts <i>et al.</i> (2015)	*	-	-	**	**	**	**	**	**	**	**	**	-	*	-	**	22
Ickmans <i>et al.</i> (2013)	*	-	**	**	**	**	**	**	**	**	**	**	-	**	**	**	27
Vermeulen and Vermeulen van Eck (2014)*	**	-	-	**	**	**	**	-	**	**	*	*	-	-	-	**	18
Hodges <i>et al.</i> (2017)	-	-	-	**	**	**	-	**	-	**	**	**	*	**	-	**	19
Moneghetti <i>et al.</i> (2018)	**	-	-	**	**	**	-	**	**	**	*	*	-	-	**	**	20

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- A score of 0 was awarded, * a score of 1 was awarded, ** a score of 2 was awarded.

5.9.4 Results of Data Synthesis

The meta-analysis revealed that the pooled mean VO_{2peak} was 5.2 (95% CI 3.8 to 6.6) $ml.kg^{-1}.min^{-1}$ *lower* in people with ME/CFS than in healthy controls. The between-study variability expressed as a standard deviation (Tau) was 3.4 (1.5 to 4.5) $ml.kg^{-1}.min^{-1}$.

The 95% prediction interval – indicating a plausible range for the effect size in a future study conducted in similar settings – was -1.9 (ME/CFS>control) to 12.2 (Control>ME/CFS) $ml.kg^{-1}.min^{-1}$. The probability that the effect in a future study would be > the minimum clinically important difference of 1.1 $ml.kg^{-1}.min^{-1}$ (Control>ME/CFS) was 0.88. The probability that the effect in a future study would be greater than the pre-defined ‘moderate’ threshold of 3.8 $ml.kg^{-1}.min^{-1}$ was 0.65.

Egger’s regression coefficient was 2.1 (95% CI, 0.2 to 3.9). The point estimate and confidence interval revealed a possible small-study effect, such that smaller studies were associated with smaller control-ME/CFS differences.

Meta-regression with study quality as the moderator demonstrated that heterogeneity was reduced slightly, with study quality accounting for 11% of the between-study variance. Higher quality was associated with a reduced magnitude of difference between groups. For a 2-standard deviation increment in quality (c. 8 points), the pooled difference (control-ME/CFS) decreased by 1.9 (-0.8 to 4.6) $ml.kg^{-1}.min^{-1}$.

5.10 Discussion

The primary finding from this systematic review and meta-analysis is that people with ME/CFS appear to have a substantially lower VO_{2peak} compared to controls. The prediction interval – capturing a plausible range of effects in a future study in similar settings – ranged from a small advantage for people with ME/CFS to a very large difference in favour of controls. Indeed, the probability (% chances) that the difference in a future study in similar settings would be larger than the minimum clinically important difference (in favour of controls) was 88%, or odds of >7:1 in favour. The point estimate for the pooled difference between controls and people with ME/CFS represented a moderate effect size, with a probability of 65% that the effect in a future study would be greater than the pre-defined moderate effect size threshold - odds of almost 2:1 in favour. It can be inferred, therefore, that the difference in peak oxygen uptake (controls-ME/CFS) is likely to be clinically relevant. The findings from this review agree broadly with the narrative synthesis reported by Nijs *et al.* (2011). However, whilst Nijs *et al.* (2011) suggested a possible reduced peak exercise capacity in people with ME/CFS, the findings from the current review are based on a greater number of papers and our meta-analysis provides stronger evidence that people with ME/CFS have a reduced VO_{2peak} versus apparently healthy controls.

Our meta-analysis revealed substantial heterogeneity of effect size, with a point estimate for between-study variability (Tau) of $3.4 \text{ ml.kg}^{-1}.\text{min}^{-1}$ – the typical variability between studies in the difference between controls and people with ME/CFS for peak oxygen uptake. The measure of study quality

explained 11% of the between-study variance, with a 2-SD increment in quality associated with a $c.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$ reduction in the pooled difference (control-ME/CFS). The confidence interval, however, revealed that the plausible range for this effect of study quality, consistent with the data and model, ranged from trivial to moderate.

Aside from a possibly small influence of study quality, the substantial between-study variance in effect size could be due to sample heterogeneity for both people with ME/CFS and controls. It is unknown whether the people with ME/CFS within the included studies are representative of the ME/CFS population. All studies included within this review have used a volunteer or convenience sampling approach, and it is plausible that those volunteering for studies involving maximal exercise testing are a more active and more physically fit sub-group of the ME/CFS population. Furthermore, the ME/CFS population is heterogeneous, with possible subgroups or phenotypes (Collin *et al.*, 2016). Identifying possible sub-groups within the ME/CFS population and any affect this might have on $\text{VO}_{2\text{peak}}$ is an important area to address in future studies.

The use of criteria used to assess if $\text{VO}_{2\text{peak}}$ has been achieved is often used as an objective measure of maximal effort and might also contribute to the between-study variance in effect size. Criteria were used in 16 papers and reported in 9 studies. 16 of the 32 studies included in this review used no criteria to assess if maximum effort had been achieved. Poole *et al.*, (2008) reported that the generally accepted criteria for assessing maximum effort in

a $\text{VO}_{2\text{peak}}$ test might underestimate $\text{VO}_{2\text{peak}}$ by 27%. Furthermore, the use of criteria secondary to achieving a plateau in VO_2 should not be used as this can result in significant underestimation of $\text{VO}_{2\text{peak}}$ in some participants or result in the assumption that some participants might not have achieved their $\text{VO}_{2\text{peak}}$ when in fact they have. This variation could mean that it was assumed that maximum effort was achieved when this was not the case and result in an under-reporting of $\text{VO}_{2\text{peak}}$. This finding was further supported by Midgley *et al.*, (2007) who reported that the current criteria used to assess maximum effort might not be sufficiently sensitive to reliably assess maximum effort and that researchers should consider assessing the psychological willingness of participants to achieve maximum and the impact this might have.

It is unclear how those with ME/CFS prepared for the maximal tests in the included studies. This issue might be important, as the anticipation of post-exertional malaise might have limited performance in the exercise test. Larun and Malterud (2011) reported that people with ME/CFS were not opposed to physical activity, but might have to adjust their expectations, prepare for activity by reducing any stress load, and find a safe and advantageous balance between activity and rest. It is fair to hypothesise that some people with ME/CFS might rest in the lead-up to an exercise test to self-manage their symptoms while others might carry out the same levels of physical activity that they would normally. This issue becomes important when trying to assess the 'cost' of physical exertion as a stressor to people with ME/CFS and subsequent limitations on tasks of daily living. This variation in physical activity leading up to a maximal test could explain some of the heterogeneity noted

within this study; however, this issue has not been explored in the current literature.

A further point to consider is the implications of symptom severity and the interaction with the duration of illness. A person with ME/CFS who has been ill for a longer duration, but with less severe symptoms, might have a different profile to a person with more severe symptoms who has not been ill for as long. This interaction between symptom severity and duration of illness has not been explored in the included studies. Some studies have reported data on duration of illness (Claypoole *et al.*, 2001; Sargent *et al.*, 2002) or stipulated an illness duration in their inclusion criteria (Sisto *et al.*, 1996; LaManca *et al.*, 2001; Cook *et al.*, 2003a) and others assessed fatigue severity (Fulcher and White, 2000; Bazelmans *et al.*, 2001; Farquhar *et al.*, 2002; Jones *et al.*, 2012) or symptom severity (Sisto *et al.*, 1996; Rowbottom *et al.*, 1998; LaManca *et al.*, 1999; Sargent *et al.*, 2002; Cook *et al.*, 2003a; Hodges *et al.*, 2017; Moneghetti *et al.*, 2018). Only one study in this review reported data on both symptom severity and illness duration (Sargent *et al.*, 2002). However, while this study reported no correlation between symptom severity and duration of illness it did not attempt to assess if the interaction between these two variables may have had an impact on VO_{2peak} . Further research is needed to address this issue.

The numerical score used within this review to provide an overview of each study's overall methodological quality could be viewed as over-simplistic. For example, when assessing the matching of controls to participants with

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ME/CFS a maximum score of 2 was awarded if cases and controls were matched irrespective of what they were matched for. Therefore, papers that used more sophisticated matching such as for level of physical activity will have received the same score as those that matched simply for age and sex.

It should be noted that the MCID used in this review was calculated using data from a population based study by Laukanen *et al.* (2016) however, it has been argued that there may be some limitation of the oxygen transport system or possible impairment of oxygen metabolism in people with ME/CFS (Hollingworth *et al.*, 2010; Vermeulen *et al.*, 2010; Tomas *et al.*, 2017; Nelson *et al.*, 2019; Missailidis *et al.*, 2019; Tomas and Elson, 2019). An individual's cardiorespiratory fitness is dependent on a number of factors (Glynn and Fiddler, 2009). These include the ability of the respiratory system to supply oxygen to the blood, the ability of the blood to carry the oxygen, the ability of the heart to pump blood to the working muscles and the ability of the muscles to uptake and utilise oxygen from the blood (Glynn and Fiddler, 2009). These factors are important when considering Fick's equation, that VO_2 is equal to cardiac output multiplied by the difference in the amount of oxygen in the arterial blood compared to venous blood (i.e. how much oxygen was extracted and used by the muscle) (Wigmore *et al.*, 2011).

It is feasible that impairment of mechanisms involved with oxygen transport and/ or oxygen metabolism may impact on the VO_{2peak} of people with ME/CFS. It should therefore be acknowledged that an MCID derived from healthy populations may be inappropriate for an ME/CFS population. Nevertheless in

the absence of any ME/CFS specific information this was deemed to be the most appropriate data to calculate a MCID.

It is important to acknowledge a number of additional limitations in the current review. First, while VO_{2peak} sets the upper limit of relatively sustainable energy expenditure, submaximal markers such as the lactate or ventilatory threshold might be regarded as a superior indicator of the capacity to carry out sustained activities of daily living than VO_{2peak} (Sargent *et al.*, 2002). Secondly, Egger's regression coefficient and its uncertainty revealed a possible small-study effect, such that smaller studies were associated with smaller control-ME/CFS differences. However, our meta-analysis revealed substantial heterogeneity and the evaluation of small study effects should be interpreted with caution. Thirdly, we have placed inferential emphasis on the prediction interval for the difference in peak oxygen uptake between controls and people with ME/CFS in a future study in similar settings. The robustness of this interval relies on a precise estimate of the between-study variance (Tau-squared), as this makes by far the largest contribution to the standard error used to construct the prediction interval around the pooled mean effect. In the current review, the confidence interval for the between-study variability was relatively wide, and caution is warranted in interpreting the prediction interval, as for most meta-analyses.

Finally, it should be noted that due to the lack of objective criteria used by a number of included studies it is unclear if the difference in VO_{2peak} noted within this review is due to those with ME/CFS not achieving their physiological

maximum. Alternatively, it is possible that participants included in these studies are a more active subgroup of the ME/CFS population which may have resulted in an overestimation of VO_{2peak} . Therefore, future studies should ensure both the use of objective criteria for maximum effort and a consideration of illness severity and activity levels when describing the included sample.

5.11 Conclusion

In conclusion, synthesis of the literature has demonstrated that people with ME/CFS appear to have a substantially lower VO_{2peak} than healthy controls. This lower exercise capacity might increase the risk of cardiovascular and all-cause mortality and affect the ability to carry out sustained activities of daily living.

Chapter 5 Commentary

Chapter 5 was published in e-first format in December 2018 and then in full print version in February 2019 (Franklin *et al.*, 2019). The article appeared to be accepted well, receiving an Altmetric score of 264 (<https://www.altmetric.com/details/52864112>, accessed 13th April 2020). Primarily this interest was through social media receiving 442 tweets from 352 twitter users. The study was posted on 6 Facebook pages and was cited on the ME Associations website as an important study published in December 2018. As of April 2020, the review had been cited in four studies.

The interest in this study appeared to be linked with a belief that the findings support a physiological mechanism of illness. Although from the a researcher's perspective it may be inappropriate to draw this conclusion from this review. Nevertheless, many members of the public, researchers and clinicians shared the review with the premise of a reduced exercise capacity supporting the hypothesis of a physiological element to the illness. As discussed above it is not clear if this reduced exercise capacity is caused by ME/CFS or by periods of inactivity as a consequence of the illness. It is also not clear if participants in these studies did indeed reach their physiological maximum and therefore the reliability of the findings can be questioned. It may be of interest to note that during the peer-review process it was requested to consider expanding on the findings however again it was felt that any speculation based on the findings of this review would be beyond the remit of the study and therefore inappropriate to do so.

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Communication from other researchers in relation to this study was also received, one highlighting issues around the use of the Oxford Criteria as a diagnostic definition and that organisation such as the Institute of Medicine in the United States had recommended retiring this case definition. The research team had discussed analysing studies using the Oxford Criteria separately however due to the low number of studies using this definition (2 of 32, only 1 using it exclusively) it was not possible to do so.

There are two further reflections from this study. The first from a research perspective; the ethical considerations of asking those with an illness, which is characterised by a significant worsening of symptoms following exercise, to exercise to maximal effort. It also raises the question of how those with significant illness, such as those bedbound would be able to participate in high intensity exercise tests. With limited empirical data demonstrating the consequences of such tests, this area should be considered in more detail.

Finally, the topic of ME/CFS could be considered relatively political. There is significant pressure on government bodies such as NICE and research organisations such as Cochrane to be more mindful of the specific nature of the condition. Changes being made by both the national guidelines and a re-write of the Cochrane review assessing GET in ME/CFS has been undertaken, however with greater input from stakeholders, including people with ME/CFS as an advisory group. The interest in finding research evidence which supports a physiological mechanism of illness appears to be readily shared and discussed on social media sites and discussion forums.

Summary of Chapter 5

This review contained a reasonable number of studies (32) which provides some weight to the conclusions that people with ME/CFS have a reduced VO_{2peak} compared to apparently healthy controls. However, from the data available no conclusions can be drawn to whether this reduction is a consequence of reduced physical activity (either due to a physiological cause or negative illness belief) or caused by the illness in a way that is not currently understood. A point of note is the poor quality of a number of the studies in this review. The meta-regression demonstrated that as study quality increased the difference between patients and controls reduced. The main factor to be addressed in studies that follow is determining if people with ME/CFS and controls truly reached their physiological maximum as this is poorly reported in the included papers. The lack of data relating to how many participants met criteria for maximum effort and with which criteria raises questions about the reliability of these findings.

Another area not addressed in the included papers and therefore not addressed in this review is the consequence of maximal effort exercise on people with ME/CFS and the symptoms in the days that follow testing. Measuring symptoms following exercise testing may provide important information about the changes in the symptoms following activity which provides important insight when developing interventions.

Chapter 6: Quantifying the variability in 24-hour repeated maximal exercise tests of peak oxygen consumption in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

6.0 Background

Chapter 5 provided evidence to support the hypothesis that people with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) have a reduced peak oxygen uptake (VO_{2peak}) and that this may increase their risk of cardiovascular and all-cause mortality. Nevertheless, what is not clear is how high intensity exercise affects the symptoms of people with ME/CFS. It is widely recognised that too much physical activity can result in a worsening of symptoms commonly referred to as post exertional malaise (PEM) (Carruthers *et al.*, 2003). What is unclear, is if high intensity exercise can result in a physiological change within those with ME/CFS, which is not demonstrated in healthy populations. This change would be of particular importance to providing an understanding of the consequences of physical activity in this group and in identifying possible objective markers that can be found in people with ME/CFS which are not present in healthy controls.

One method used to explore the above change is the use of provocation studies (Komaroff, 2019), which involve participants partaking in two repeated VO_{2peak} tests separated by 24 h (The Institute of Medicine, (IOM) 2015). To date, research evidence assessing VO_{2peak} in repeated maximal exercise tests is equivocal. Two research groups have demonstrated that people with ME/CFS have a reduced VO_{2peak} on their second test while controls

demonstrated improvement (VanNess *et al.*, 2007; Vermeulen *et al.*, 2010). Two other research groups demonstrated a reduced VO_{2peak} in both the ME/CFS group and the control group (Snell *et al.*, 2013; Nelson *et al.*, 2019). While in another study, an improvement in both the ME/CFS group and the control group in the second test was reported (Hodges *et al.*, 2018). Also, Nelson *et al.*, (2019) reported no difference in VO_{2peak} between people with ME/CFS and controls over the two tests. Yet, they reported that work rate (WR) at anaerobic threshold (AT) was lower in people with ME/CFS but not in controls in the second of the two exercise tests, indicating that it may be the change in WR at AT and not the change in VO_{2peak} , which is the variable of interest.

Investigating the impact of high intensity exercise on physiological outcomes may provide useful information in the understanding of ME/CFS. Nevertheless, to date, there are no systematic reviews or meta-analyses which have aimed to synthesise the findings from these studies. It is therefore the aim of this review to explore the variability in VO_{2peak} and WR over two maximal exercise tests separated by 24 h in people with ME/CFS compared to apparently healthy controls.

6.1 Aim of this review

The primary aim of this review is to quantify the size of the difference in the change in VO_{2peak} between people with ME/CFS vs apparently healthy controls in two exercise tests separated by 24 h.

The secondary aim of this review is to quantify the size of the difference in the change between people with ME/CFS vs apparently healthy controls in two exercise tests conducted 24hrs apart for the following variables:

- a. VO_2 at AT
- b. WR at peak
- c. WR at AT

6.2 Design

The research design used in this study was a systematic review of observational studies and included meta-analyses.

This review was registered in the Prospero register for systematic reviews (CRD42019117837)

(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=117837)

There were three changes from the original protocol: 1) Original intent was to assess the variability of the change between the two groups however due to the small number of studies and the large confidence interval around the estimate of the pooled mean difference this was not conducted. 2) The meta-analyses assessing the difference in $\text{VO}_{2\text{peak}}$ between people with ME/CFS and controls at test 1 and a separate analysis at test 2 was not conducted due to retrieving only a small number of studies. 3) Only three studies reported data relating to heart rate and we deemed this number too low to reliably meta-analyse change in heart rate. This decision was informed by Röver *et al.*

(2015) that meta-analyses with ≤ 3 papers substantially increases the risk of a type I error, especially when the precision of the included studies varies. The PRISMA guidelines were used in the reporting of this review (Liberati *et al.*, 2009).

6.3 Criteria for selecting studies

The eligibility criteria for this review were:

Exposure. Adults (over 18 years old) with any clinical diagnosis of ME/CFS using any recognised diagnostic definition including; the Canadian Criteria (Carruthers *et al.*, 2003), International Consensus Criteria (ICC) (Carruthers *et al.*, 2011), Fukuda *et al.*, (1994) and Holmes *et al.*, (1988). To be included, studies were required to compare people with ME/CFS with apparently healthy controls.

Outcome. Any study that assessed VO_{2max} or VO_{2peak} as a maximal test was included. Studies were required to include two VO_{2peak} tests separated by 24 hours. Studies must have collected data on expired air to be included and were excluded if a predicted VO_{2peak} was calculated from other variables or from a submaximal test. Studies had to include the primary outcome (VO_{2peak}) to be included, data pertaining to the secondary outcomes was then extracted from these papers.

Types of study. Any observational study was included. Studies were required to be published in a peer-reviewed journal with a description of the data collection methods.

6.4 Search strategy

A comprehensive literature search was conducted from inception to March 2019 of CINAHL, PubMed, PsycINFO, Web of Knowledge, Embase, Scopus and Medline. The comprehensive search strategy was peer reviewed by a Senior Librarian at Teesside University to ensure its accuracy and effectiveness at retrieving appropriate studies. The following search terms and strategy (involving Boolean operators) were utilised:

(MH "Fatigue Syndrome, Chronic") OR "myalgic encephalo*" OR "CFS" OR "ME" OR "CFS/ ME"

AND

"Repeated"

AND

"VO₂peak" OR (MH "Aerobic Capacity") OR "VO₂" OR "oxygen uptake" OR "maximal oxygen uptake" OR "maximal oxygen consumption" OR (MH "Oxygen Consumption")

As well as searching online databases, reference lists were checked. Grey literature was not included, as papers were required to be peer reviewed to be included. During the searching process a number of grey literature studies were identified and the authors were contacted directly to assess if this data had been published. Following discussions with authors, it became clear that the published versions of this data were already retrieved in the literature search and therefore this process retrieved no new papers.

6.5 Selection of studies

Selection of studies was conducted in two stages. The first was based on title and abstract and this was recorded as a 'yes' if all inclusion criteria stated above were met, a 'maybe' if it was unclear if all criteria was met and a 'no' if any of the criteria was not met. Following this process those studies deemed to be a yes or maybe were assessed in the second selection process which involved reading the full text. The first and second selection was conducted by JF. Following the second selection process a discussion took place between the three reviewers regarding the suitability of the final papers. A consensus was then reached on the final papers for inclusion.

6.6 Assessment of methodological quality

To assess the quality of the included papers the Systematic Appraisal of Quality for Observational Research (SAQOR) framework (Ross *et al.*, 2011) was used. This framework was modified as described in chapter 5, pg. 47-49. The assessment of methodological quality was assessed by JF. Each paper was scored twice and then the scores were checked for consistency. A discussion took place between the three researchers on aspects of the design to agree the key features to focus on to ensure consistency across all papers.

6.7 Data Extraction

Sample size, VO_{2peak} , VO_2 at AT, WR at peak and WR at AT was extracted from each paper and inputted directly in Microsoft Excel. For the analysis the aim was to assess the difference in the mean change in VO_{2peak} between test

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1 and test 2 (test 2 VO_{2peak} minus test 1 VO_{2peak}) between people with ME/CFS and controls. To conduct the meta-analysis the mean change and the standard deviation (SD) of the change was required for both the ME/CFS and control groups (Higgins and Green, 2011). One of the included papers reported this data (Vermeulen *et al.*, 2010). For the remaining studies, authors were contacted directly and asked to provide this data. Two authors provided this information (Hodges *et al.*, 2017; Nelson *et al.*, 2019) however, for two papers the SD of the change was estimated using the method described by Higgins and Green (2011) section 16.1.3.2. Table 6.1 provides a summary of the authors who were contacted for the purposes of this review. Estimation of the change SDs involved firstly calculating a correlation coefficient for a study that provided a change SD. As this describes how similar the baseline and final measurements were across participants (Higgins and Green, 2011). This correlation coefficient can then be used to estimate the SD of the change in the remaining paper. Correlation coefficients were calculated for Vermeulen *et al.*, (2010) ($Corr_{CFS}$ 0.96; $Corr_{Con}$ 0.98), Hodges *et al.*, (2017) ($Corr_{CFS}$ 0.94; $Corr_{con}$ 1.00) and Nelson *et al.*, (2019) ($Corr_{CFS}$ 0.97; $Corr_{con}$ 0.96). For a full overview of the calculations and workings, see appendix D pg. 310.

Table 6.1; Researchers contacted during data extraction

Study Researcher (Email)	Information requested	Response
Nelson <i>et al.</i> (2019) Dr Max Nelson (Max.Nelson@unisa.edu.au)	Mean change and change SD for all	All data requested was provided

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	variables for Nelson <i>et al.</i> (2019)	
Hodges <i>et al.</i> (2017) Dr Lynette Hodges (L.D.Hodges@massey.ac.nz)	Mean change and change SD for all variables for Hodges <i>et al.</i> (2017)	All data requested was provided
VanNess <i>et al.</i> (2007) Professor Mark VanNess (mvanness@PACIFIC.EDU)	Mean change and change SD for all variables for VanNess <i>et al.</i> (2007)	Researcher responded to emails however it was not possible to provide change SD.
Lien <i>et al.</i> (2019) Katarina Lien (katarinalien@gmail.com)	Mean change and change SD for all variables for Lien <i>et al.</i> (2019). Query figure 5D.	Responded to email however data was not provided and query was not clarified.
Vermeulen <i>et al.</i> (2010) Ruud Vermeulen (rv@cvscentrum.nl)	Queried the accuracy of the change data for HR for the control group	No response
Snell <i>et al.</i> (2013) Christopher Snell (csnell@pacific.edu)	Requested mean change and SD change for both groups	No response

The statistics from Vermeulen *et al.*, (2010) were more conservative than those stated by Hodges *et al.*, (2017) and the Nelson *et al.*, (2019) data was not available until later in the meta-analysis process. Therefore the correlation coefficients derived from Vermeulen *et al.*, (2010) were used to calculate the SDs of the change in the remaining papers using the formula in Higgins and Green (2011) section 16.1.3.2. The mean change and SD of the change for Lien *et al.*, (2019) were presented in figures and extracted using the Digitizelt

computer programme (Digitizelt, 2017) and inputted directly into the data extraction spreadsheet.

For data relating to VO_2 at AT, WR at peak and WR at AT the correlation coefficients were calculated using the same method as described above and can be found in table 6.1. The final dataset that was inputted into the meta-analyses can be found in table 6.2 and 6.3.

Although the process used to estimate the SDs of the change is based on the methods described by Higgins and Green it must be acknowledged that these are only estimates and not the true SDs of the change for these studies. Higgins and Green (2011) stated that these methods should be used carefully, as there is no way of ensuring that the calculated correlation coefficients are accurate and they may be affected by factors such as the characteristics of the participants themselves. However, for the purpose of this analysis the most important statistic was viewed to be the change in the outcomes over the 24 hrs. However, the limitations of estimating the SD of the change should be considered when interpreting the results of the analysis.

Table 6.2; Correlation coefficients used to calculate the SDs of the change

Variable	ME/CFS Correlation coefficient	Control Correlation coefficient
$\text{VO}_{2\text{peak}}$	0.96*	0.98*
VO_2 at AT	0.82*	0.82*
Peak WR	0.95*	0.93*

WR at AT

0.92*

0.79*

 *Calculated using data from Vermeulen *et al.*, (2010)

6.8 Data Analysis

Mean change and SD of the change for the four variables and the sample sizes were inputted into Comprehensive Meta-Analysis Software version 3 (CMA) in duplicate for data analysis. A random effects meta-analysis was conducted. Due to the small number of studies included within this review the DerSimonian and Laird (methods of moments) estimator with a t-distribution (Knapp and Hartung) was applied to assess heterogeneity. Importantly, the Knapp and Hartung method calculates the confidence interval from a t-distribution to estimate the distribution of possible effects (Jackson *et al.*, 2017) as opposed to using a z-distribution which assumed a normal distribution and infinite sample size (IntHout *et al.*, 2014). IntHout *et al.* (2014) stated that the standard DerSimonian and Laird method (z-distribution) consistently demonstrates false positives especially when the number of studies is less than twenty. Notably, when using a small number of studies, a wider confidence interval is needed to reflect the uncertainty in the between study variance (Jackson *et al.*, 2017) which is more effectively provided using the Knapp and Hartung (t-distribution) approach. Due to these reasons the Knapp and Hartung method is consistently viewed as a more precise approach when the number of studies is < 20 and specifically when the number of studies ≤ 5 (IntHout *et al.*, 2014; Röver *et al.*, 2015; Jackson *et al.*, 2017).

Although five of the included papers provided WR at AT data, only four of these studies were included in this analysis. The information provided relating to

change in WR at AT in Lien *et al.*, (2019) (in Figure 5(D) of this paper) displayed 2 results at +10W, 2 results at -10W and the remaining values on exactly 0W. These results seemed highly improbable and therefore the Lien research team were contacted directly to clarify these findings. However, this data was unable to be verified with the Lien research group and therefore this data set was excluded from the analysis. The data for the other variables in this paper were extracted and included in the other analyses.

To estimate the magnitude of the effect the standardised mean difference (SMD) was calculated by dividing the pooled mean by the pooled SD, generating a Cohen's d statistic which reports the effect size in standard deviation units (Vacha-Haase and Thompson, 2004). This was calculated using the test 1 ME/CFS group SD for the respective variable. This allowed the generation of a statistic for the change from test 2 to test 1 in ME/CFS vs. controls in relation to the variability in the ME/CFS group. The pooled SD was calculated by meta-analysing the variance and the standard error (SE) of the variance derived using the formula described in Hopkins (2015) ($SE \text{ of variance} = \sqrt{(2 \cdot sd^4)/df}$). The point estimate (pooled variance) was then converted to an SD (Hopkins, 2015). SMD was interpreted as 0.2 a small effect, 0.5 a moderate effect and 0.8 or greater is equal to a large effect (Vacha-Haase and Thompson, 2004).

When defining a clinically relevant threshold, data was available for WR at AT, in Nelson *et al.*, (2019) which provided a range of between 7.5W and 12.5W and appeared to provide a reasonable degree of sensitivity and specificity.

However, there was uncertainty where on this range to apply a point estimate for a clinically relevant threshold. As a second method it was hypothesised that half an SD may be useful in providing an estimate to be used alongside the data generated in Nelson *et al.*, (2019). Half SD estimates have been useful in defining the MCID in previous studies and has been equivalent to MCID derived from anchor-based methods (Farivar *et al.*, 2004). However, Sloan (2005) reported that half the SD can be useful in providing a simple foundation, but caution should be taken when using this method alone. Therefore this method was applied to provide a general estimate of MCID to be used in conjunction with the data from Nelson *et al.*, (2019).

Half an SD for the pooled data was 10.9 W; similar findings to the centre of the range provided by Nelson *et al.*, (2019). As there was a satisfactory level of agreement between the two methods, the research team agreed that the midpoint from Nelson *et al.*, (2019) provided an appropriate point estimate for the MCID threshold for this review. Therefore, the MCID for WR at AT defined in this review was a difference in the mean change between people with ME/CFS and controls of 10W. As no other data was available to calculate an anchor based MCID for the other variables these were not defined in this review. As supported by Farivar *et al.*, (2004) that multiple anchors should be used to estimate an MCID of an unknown quantity of change.

A prediction interval was calculated to provide a range of the likely effects in a future study conducted in similar settings (Int'Hout *et al.*, 2016). Using the methods described by Mathur and VanderWeele (2018) the proportion of

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future studies was calculated which would exceed the MCID (10 W) for WR at AT.

Table 6.3; Data inputted into meta-analysis for difference in change VO_{2peak} and WR at peak between people with ME/CFS and controls

Study	Sample size ME/CFS	Sample Size Control	Change in VO_{2peak} ($ml.kg^{-1}min^{-1}$)		Change in Work rate (W)	
			Mean difference (SD) ME/CFS	Mean difference (SD) control	Mean difference (SD) ME/CFS	Mean difference (SD) control
Vermeulen <i>et al.</i> , (2010)	15	15	-1.33 (1.68)	0.73 (1.39)	-6.3 (11.5)	11.1 (18.3)
Hodges <i>et al.</i> , (2017)	10	10	1.32 (3.04)	1.08 (1.25)	-9 (14.1)*	3 (15.2)*
VanNess <i>et al.</i> , (2007)	6	6	-5.76 (3.23)*	0.47 (1.72)*	-	-
Snell <i>et al.</i> , (2013)	51	10	-1.07 (1.27)*	-1.08 (0.88)*	-7.94 (9.68)*	2.8 (8.91)*
Nelson <i>et al.</i> , (2019)	16	10	-0.11 (2.07)	-0.38 (1.74)	-1.9 (10.5)	2 (3.5)
Lien <i>et al.</i> , (2019)	18	15	-1.44 (1.04)	-0.93 (1.68)	-6.97 (7.18)	-4.27 (6)

Data for VO_{2peak} and work rate reported as the change in mean difference (test 2 minus test 1) and standard deviation of the change. *Change SD has been estimated. - data not available in study.

Table 6.4; Data inputted into meta-analysis for difference in change $\text{VO}_{2\text{peak}}$, WR at AT between people with ME/CFS and controls

Study	Sample size ME/CFS	Sample Size Control	Change in VO_2 ($\text{ml.kg}^{-1}\text{min}^{-1}$)		Change in Work rate (W)	
			Mean difference (SD) ME/CFS	Mean difference (SD) control	Mean difference (SD) ME/CFS	Mean difference (SD) control
Vermeulen <i>et al.</i> , (2010)	15	15	-0.87 (1.77)	1.07 (2.63)	-4.4 (9.66)	7.67 (19.5)
Hodges <i>et al.</i> , (2017)	10	10	1.27 (2.6)*	4.9 (7.3)*	-12 (15.16)*	13 (26.17)*
VanNess <i>et al.</i> , (2007)	6	6	-4 (1.87)*	0.45 (3.01)*	-	-
Snell <i>et al.</i> , (2013)	51	10	-1.38 (0.82)*	0.29 (1.87)*	-27.31 (8.1)*	5.5 (11.98)*
Nelson <i>et al.</i> , (2019)	16	10	-0.51 (1.59)	-0.64 (1.05)	-15.3 (11.9)	-2.5 (3.5)
Lien <i>et al.</i> , (2019)	18	15	-	-	-7 (9.96)	Query

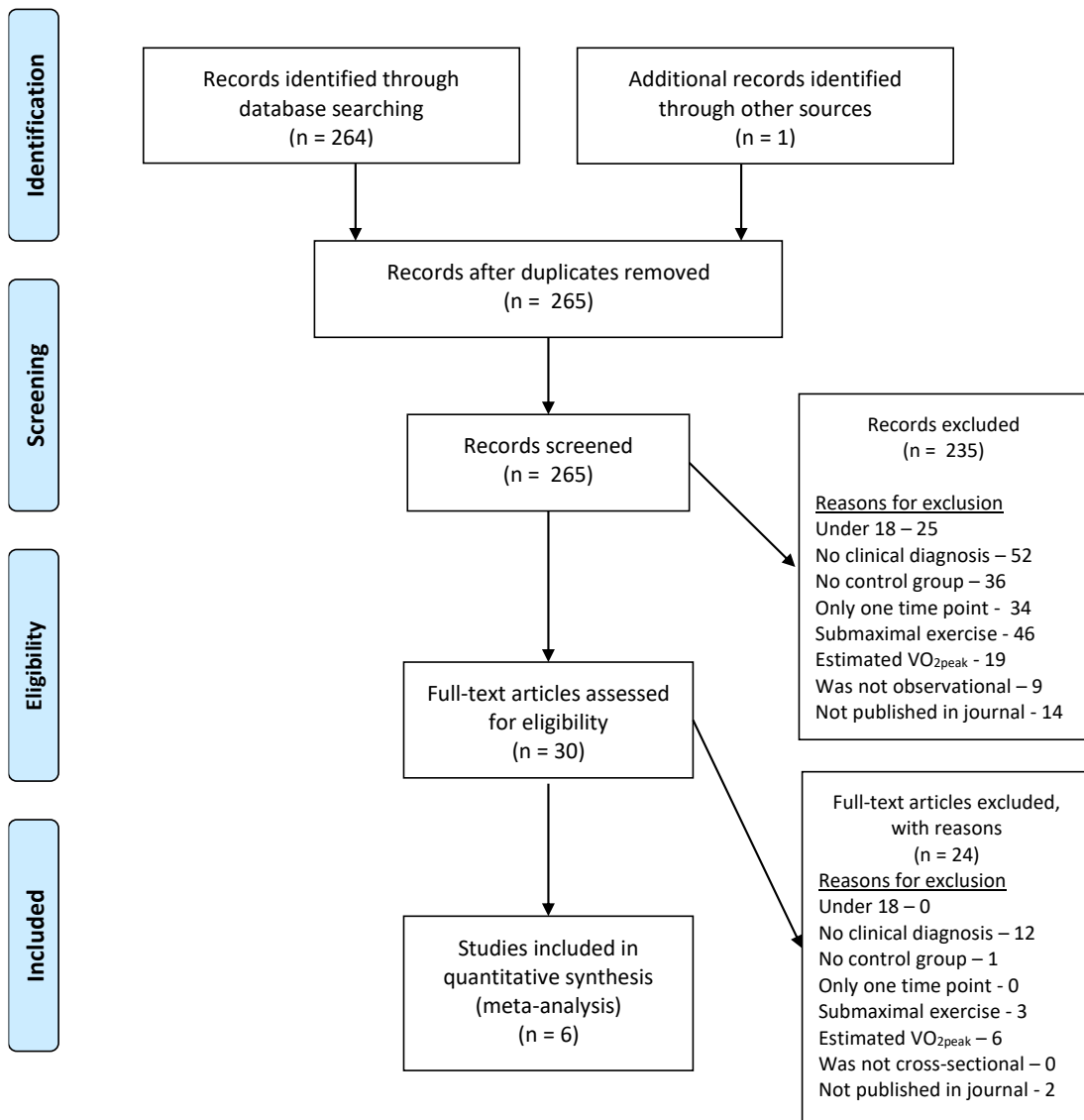
Data for $\text{VO}_{2\text{peak}}$ and work rate reported as the change in mean difference (test 2 minus test 1) and standard deviation of the change. *Change SD is estimated. Query – the accuracy of the data presented in the study is questionable. - data not available in study.

6.9 Results

6.9.1 Results of the search

The comprehensive literature search yielded 265 papers in total; 264 through searching electronic databases and 1 through hand searching. Following the first selection of studies, 30 papers were assessed for eligibility to include in the study. This was reduced to six papers after the second selection. An overview of the selection process can be seen in figure 6.1.

Figure 6.1; PRISMA diagram illustrating the selection of studies



6.9.2 Summary of included papers

Table 6.5 provides a summary of the included papers. Five of the included papers used Fukuda as a diagnostic definition, however Hodges *et al.*, (2017) and Nelson *et al.*, (2019) also required patients to meet the Canadian and ICC definitions. Lien *et al.*, (2019) used the Carruthers *et al.*, (2003) diagnostic definition. The six papers performed a VO_{2peak} test using a cycle ergometer except for two participants with ME/CFS in VanNess *et al.*, (2007) All papers

included healthy and/ or sedentary control group however two papers Vermeulen *et al.*, (2010) and Lien *et al.*, (2019) did not match for any characteristics.

6.9.3 Overview of assessment of methodological quality

Table 6.4 provides a summary of the methodological quality score for included papers. However, a full overview of the quality assessment can be found in appendix E pg. 316. The quality scores for the six papers ranged from 14 to 24 with VanNess *et al.*, (2007) having the lowest quality score and Nelson *et al.*, (2019) having the highest score. With regard to the overview of the ME/CFS group, although five of the six papers provided information about the source of the sample, only one paper gave any information about the sampling process, sample size was calculated in one of the six studies. The six papers all provided a good overview of the inclusion and exclusion criteria. All papers included a comparison group, and this was easily identifiable from the patient group. The source of the control group was reported in two of the included papers. Matching for any characteristics was conducted in four of the six studies (VanNess *et al.*, 2007; Snell *et al.*, 2013; Hodges *et al.*, 2017; Nelson *et al.*, 2019), two papers did not assess for any statistical differences between the two groups (VanNess *et al.*, 2007; Hodges *et al.*, 2017).

The assessment of the exposure (ME/CFS) was good in all six papers. Assessment of the outcome (VO_{2peak}) was good in four of the six papers (Snell *et al.*, 2013; Hodges *et al.*, 2017; Lien *et al.*, 2019; Nelson *et al.*, 2019). The assessment of the outcome was poor in VanNess *et al.*, (2007). The

description of the maximum effort test was good in three papers and adequate in three papers. Four of the four papers discussed the use of criteria (or a measure) to assess maximum effort however only two papers provided specific detail about what the criteria for assessing maximum effort was. Information on how many participants achieved each criteria is not reported in any of the included papers. Three papers provided a good overview of controlling for other possible extraneous variables. Missing data was not discussed in five of the papers. Five papers provide an adequate overview of the results, only one paper reported the change data between test 1 and test 2, the overview of the results was scored as poor in Lien *et al.* (2019).

Table 6.5; Summary of the assessment of methodological quality

Question	Vermeulen <i>et al.</i> , (2010)	Hodges <i>et al.</i> , (2017)	VanNess <i>et al.</i> , (2007)	Snell <i>et al.</i> , (2013)	Nelson <i>et al.</i> , (2019)	Lien <i>et al.</i> , (2019)
Source of sample is clear	Good	Not Reported	Adequate	Adequate	Adequate	Adequate
Sampling method is described	Not reported	Not reported	Adequate	Not reported	Not reported	Not reported
Power analysis conducted	Not reported	Not reported	Not reported	Not reported	Not reported	Good
Entry criteria justified	Good	Good	Good	Good	Good	Good
Control group included	Good	Good	Good	Good	Good	Good
Control group identifiable	Good	Good	Good	Good	Good	Good
Source of controls explained	Not reported	Not reported	Not reported	Not reported	Good	Adequate
Controls are matched	Not reported	Good	Good	Good	Good	Not reported
Stat. sig. cases vs. controls	Good	Not reported	Not reported	Good	Good	Good

Exploring the Relationship between Physical Activity and ME/CFS

Overview of exposure	Good	Good	Good	Good	Good	Good
Adequate measure of outcome(s)	Adequate	Good	Poor	Good	Good	Good
Description of exercise test	Adequate	Good	Adequate	Good	Good	Adequate
Criteria for max effort	Not reported	Adequate	Poor	Adequate	Adequate	Not reported
Control of extraneous variables	Not reported	Good	Good	Not reported	Good	Adequate
Explanation of missing data	Not reported	Not reported	Not reported	Not reported	Not reported	Adequate
Accuracy of results	Adequate	Adequate	Adequate	Adequate	Adequate	Poor
Total score	15	18	14	20	24	19

Scoring: 'Not reported/ Poor' resulted in a score of 0, 'Adequate' resulted in a score of 1, 'Good' resulted in a score of 2. Maximum score 32.

Exploring the Relationship between Physical Activity and ME/CFS

Table 6.6; Summary of included papers

Study	ME/CFS diagnostic criteria	ME/CFS: Control Sample size %Female	Controls defined as	ME/CFS and controls matched for	Description of VO _{2peak} test	Results of study VO _{2peak} (ml.kg ⁻¹ ml ⁻¹) Mean ± SD Change data is included if reported in study
Vermeulen <i>et al.</i> , (2010)	Fukuda	15:15 100%	Healthy sedentary	-	Performed on cycle ergometer 3 mins without activity, 3 mins of unloaded pedalling, followed by pedalling against increasing resistance until exhaustion. Criteria used to assess if maximum effort was achieved is not described	CFS/ME Test 1: 22.3 ± 5.7 Test 2: 20.9 ± 5.5 Change: -1.33 ± 1.68 Controls Test 1: 31.2 ± 7.0 Test 2: 31.9 ± 7.4 Change: 0.73 ± 1.39
Hodges <i>et al.</i> , (2017)	Fukuda and Canadian and ICC	10:10 82%	Gender and age match healthy controls	Age and gender	Cycled on a cycle ergometer at between 50 and 80 rpm. Starting at 15 W load increased by 15 W/min. Criteria for maximum effort was voluntarily termination by the participant or when they were unable to maintain a pedal rate of 50 rpm, or the ACSM termination criteria were met.	CFS/ME Test 1: 24.95 ± 8.9 Test 2: 26.27 ± 7.78 Controls Test 1: 31.99 ± 10.88 Test 2: 33.06 ± 12.5
VanNess <i>et al.</i> , (2007)	Fukuda	6:6 100%	Sedentary female controls	Sex	CFS/ME patients performed either a modified Bruce treadmill protocol or a 10W/min ramping protocol on a cycle ergometer. Controls completed a 20W/min ramping protocol on a cycle ergometer. Criteria used to assess if maximum effort was achieved is not described	CFS/ME Test 1: 26.23 ± 4.92 Test 2: 20.47 ± 1.80 Controls Test 1: 28.43 ± 7.27 Test 2: 28.90 ± 8.06

Exploring the Relationship between Physical Activity and ME/CFS

Snell <i>et al.</i> , (2013)	Fukuda	51:10 100%	Sedentary controls	Age and BMI	3 mins rest followed by 1 min unloaded cycling. Participants were required to maintain 60 to 80 rpm. Workload increased by 5 W/s (15 W/min). Criteria for maximum effort: RER \geq 1.1 as well as one of the following; 1) plateau in oxygen consumption 2) rating perceived exertion $>$ 17 3) heart rate $>$ 85% age predicted max. Reported that all participants achieved RER \geq 1.1 however data is not provided.	CFS/ME Test 1: 21.51 \pm 4.09 Test 2: 20.44 \pm 4.47 Controls Test 1: 25.04 \pm 4.41 Test 2: 23.96 \pm 4.30
Nelson <i>et al.</i> , (2019)	Fukuda and Canadian and ICC	16:10 53.85%	Healthy participants	Age, BMI, physical activity status	Seated rest for 4-6 mins. Commence cycling a self-selected cadence for 5mins at 40W for males and 30W for females. Workload increased by 5W/ 20s until exhaustion. Criteria for maximum effort: required to meet at least two of the following 1) achieve at least 90% age predicted max HR 2) RER $>$ 1.1 3) RPE \geq 17.	CFS/ME Test 1: 27.3 \pm 9.2 Test 2: 27.4 \pm 8.8 Controls Test 1: 29.9 \pm 6.1 Test 2: 30.3 \pm 6.2
Lien <i>et al.</i> , (2019)	Carruthers et al (2003)	18:15 100%	Healthy control participants	-	Designed for test to last between 8-12mins. Rate varied based on demographics. Protocol – 2mins rest, 2mins unloaded pedalling at 60-75rpm. Linear increase in power till exhaustion or couldn't maintain 45rpm. Criteria used to assess if maximum effort was achieved is not described	Change data was extracted using digitizing software. Test 1 and test 2 data reported in figures only

W – Watts. Rpm – revolutions per minute. RER – respiratory exchange ratio. ACSM – American College of Sports Medicine.

6.9.4 Results of data synthesis

The data generated from the meta-analyses and used in calculating the prediction intervals and proportion of future studies are summarised in table 6.6.

The pooled mean difference of the change in VO_{2peak} over 24 hours between people with ME/CFS and controls was -1.03 (95%CI -3.23 to 1.17) $ml.kg^{-1}min^{-1}$. Indicating that people with ME/CFS had a lower VO_{2peak} at test 2 compared to test 1 ($d = -0.23$). Tau - which provides an estimate of the between study variation - was 1.29 , which demonstrates substantial heterogeneity. The 95%PI (-5 to 3) $ml.kg^{-1}min^{-1}$ demonstrates a wide range of possible effects from favouring ME/CFS to favouring controls with no clear indication of the direction of the difference.

The pooled mean difference in WR at peak exercise was $-7.95W$ (95% CI -15.25 to -0.64), indicating people with ME/CFS have a reduced peak WR at in the second test compared to controls ($d = -0.26$). Tau was 4.29 , the 95%PI (-21.9 to 6.03). VO_2 at AT was -1.66 (95%CI -3.67 to 0.36) $ml.kg^{-1}min^{-1}$, Tau was 1.18 , the 95%PI (-5.51 to 2.19), the effect size for this difference was moderate ($d = -0.55$).

Table 6.7; Overview of statistics generated from meta-analysis used to calculate 95% PI and proportion of future studies

Outcome (no. of studies)	Pooled mean	Pooled SD	SE	Tau	Tau ²	SE of Tau ²	MCID	SMD (Cohen's d)
VO _{2peak} (n=6)	-1.03	4.4	0.85	1.29	1.67	1.50	Not defined	-0.23
Peak WR (n=5)	-7.95	30.9	2.63	4.29	18.44	24.00	Not defined	-0.26
VO ₂ AT (N=5)	-1.66	3.0	0.73	1.18	1.39	1.72	Not defined	-0.55
WR AT (n=4)	-20.64	21.8	6.38	11.46	131.43	142.33	10W	-0.95

SE – standard error. SMD – standardised mean difference (Cohen's d). VO_{2peak} (ml.kg⁻¹min⁻¹). Peak WR – peak work rate (W). VO₂ AT – VO₂ at anaerobic threshold (ml.kg⁻¹min⁻¹). WR AT – work rate at anaerobic threshold (W).

The difference in WR at AT was -20.64 (95%CI -40.95 to -0.33)W, demonstrating that people with ME/CFS had a reduced power output at AT in the second of the two tests compared to apparently healthy controls (Tau = 11.46). The effect size for this difference was large (d = -0.95) providing evidence that WR at AT effectively discriminates between ME/CFS and controls. The 95%PI (-62.39 to 21.11) indicated a high degree of uncertainty. The proportion of future studies that would report an effect above the MCID (10W) can be estimated at 82% (95%CI 44% to 100%) in favour of controls.

6.10 Discussion

Results from this review demonstrated a marginal decrease in the pooled point estimate of VO_{2peak} in people with ME/CFS compared to apparently healthy controls of approximately 1 ml.kg⁻¹min⁻¹. However, the 95%PI provided no conclusions to the direction of the difference between people with ME/CFS and controls in a future study. Therefore, it can be concluded that the difference in the change in VO_{2peak} between people with ME/CFS and

apparently healthy controls in two maximal exercise tests separated by 24hrs is not clinically relevant. Based on the pooled effect of six papers it was also concluded that VO_{2peak} is not effective in discriminating between people with ME/CFS and controls.

Nevertheless, findings from this review support the hypothesis that WR at AT is reduced in the second of two tests in people with ME/CFS compared to controls. The SMD was large, almost 1 standard deviation indicating that WR at AT effectively differentiates between people with ME/CFS and controls. Further still, it is estimated that 82% of future studies assessing WR at AT between people with ME/CFS and controls will demonstrate a difference greater than the MCID of 10W - in favour of controls (i.e. the WR in people with ME/CFS reducing in the second of the two tests). These findings support those of Nelson *et al.*, (2019) that change in WR at AT may provide an objective marker for ME/CFS.

A possible mechanism for this decrease in WR at AT, at test 2 was described in Vermeulen *et al.*, (2010) that people with ME/CFS may have a limited oxygen transport capacity which would explain an increase in anaerobic metabolism in the second test. A further possible explanation was discussed by Tomas *et al.*, (2019) that people with ME/CFS may have a reduced aerobic respiratory capacity which results in transferring the cells towards anaerobic energy sources to fulfil energy demands. Tomas *et al.*, (2019) stated that evidence indicated for someone with ME/CFS, mitochondrial dysfunction may be a contributing factor to their symptoms.

While the mechanism which resulted in the reduced WR at test 2 is unclear, data from this review suggests that in the 24 hrs following high intensity exercise people with ME/CFS are unable to achieve the same WR at AT that they had 24hrs earlier. Further to this, these results would appear to demonstrate a physiological response in the 24 hrs that follow high intensity exercise in people with ME/CFS but not controls, which could be related to PEM. However, this requires exploring in more detail to fully understand the mechanisms which cause this reduction and how this relates to ME/CFS symptoms.

Although this review demonstrated a difference in WR at AT, VO_{2peak} did not differ between the two tests. A possible explanation for this, could be the methods used for measuring peak exercise. The method used to assess maximum effort was only described in detail in three of the six papers (Snell *et al.*, 2013; Hodges *et al.*, 2017; Nelson *et al.*, 2019) however the data for demonstrating how many participants met which criteria was not reported in any of the papers. It is therefore difficult to establish if the difference reported in this review is accurate or due to participants not achieving their true physiological maximum during testing.

Methods to assess maximum effort such as an inability to maintain a particular pedal rate as in Hodges *et al.*, (2017) or a particular power output has also been criticised as this may be due to lack of effort, rather than an indication of maximum effort (Midgley *et al.*, 2007). Another area to study could be to

assess subject's willingness and perceived ability to give maximal effort prior to each test (Midgley *et al.*, 2007). Indeed, Poole and Jones (2017) argued that even using criteria for maximum effort could underestimate $\text{VO}_{2\text{peak}}$ by 30-40% due to individual variations, and achieving true peak is limited to those who are familiar with the protocol and are highly motivated.

Importantly, a maximal exercise test cannot discriminate among subjects who cease exercise because of lack of motivation, perceived discomfort, or any other reasons, none of which are related necessarily to their maximal rate of O_2 transport/utilisation (Poole and Jones, 2017). However, a strength of the findings of this review is that the AT is not dependent on motivation and is more of an objective marker than peak exercise. Therefore, there may not be a need for people with ME/CFS to exercise to peak to produce this response. In this instance it would instead be important to know the lowest demand needed to produce a measurable response in people with ME/CFS. Testing at lower exercise intensities which would continue above the AT but terminate before peak exercise maybe a possible direction for future studies. This may also place less demand on those with ME/CFS and possibly widen recruitment to studies.

The ethical considerations of inviting people with ME/CFS, an illness characterised by PEM, to participate in repeated maximal exercise tests should also be considered, an argument noted in Snell *et al.* (2013). Currently there is insufficient information relating to the impact of ME/CFS symptoms following testing of this nature and the timeframe of any exacerbation of

symptoms. Therefore, as well as investigating tests that involve termination at lower exercise intensities it may also be useful to explore other exercise modalities. Nacul *et al.* (2018) reported that people with ME/CFS demonstrated a greater reduction in hand grip strength during 3 repeated tests of 3s separated by 30s when compared to apparently healthy controls. This may demonstrate a greater 'fatigability' in people with ME/CFS. Other variables which have not been assessed in these tests and this population such as electromyography (EMG) may also be useful in assessing whether a decrease in force and power that accompanies fatigue is associated with a loss of muscle activation.

Only one of the included papers (Nelson *et al.*, 2019) described using any method of familiarisation with the test. This is important to control for any learning effect which could result in an improvement in test 2 due to experience with the test rather than any physiological improvement. This was reported in Poole and Jones (2017) that VO_{2peak} may be overestimated in repeated testing as the subject gains experience and possibly enhanced confidence and therefore the accuracy of the initial VO_{2peak} is questionable.

Although these results provide information relating to possible measurable differences in WR at AT between people with ME/CFS and apparently healthy controls, the following limitations should be noted. 1) The high degree of uncertainty around the pooled mean difference in the change in WR, demonstrated by the wide 95% prediction interval – ranging from a possible larger reduction in WR in people with ME/CFS at test 2 compared to controls

(-62W) to a reduction in WR in the control group at test 2 but not the ME/CFS group (21W). 2) The large heterogeneity estimated with Tau. 3) The estimates in this review are made using a limited number of studies and only four papers (effects) were meta-analysed to estimate the pooled mean difference for change in WR at AT. 4) The SD of the change was estimated in two of the studies which will affect the precision of the pooled effect. Therefore, caution is recommended when interpreting these findings and it must be acknowledged that these results require verifying by much larger, well powered studies.

In relation to the included studies the methods used to assess maximum effort was not described in three of the six papers and none of the included papers reported this data. Lack of familiarisation with the testing procedure provides uncertainty of the impact of any learning effect. It may be of use to explore repeated sub-maximal tests to assess if this response can be measured at lower exercise intensities.

Another study by Davenport *et al.* (2020) was published during the write-up period of this thesis. This paper demonstrated that WR at AT improved by 5W in apparently healthy controls and in ME/CFS their work rate decreased by -5.4W (difference between groups of -10.4W in favour of controls). Inclusion of this paper would increase the number of included studies for this analysis to 5. As this data also includes heart rate, a meta-analysis assessing heart at AT and peak could also be conducted. Therefore future work will include this study in the analysis before submitting for publication.

6.11 Conclusion

Results from this review demonstrated that people with ME/CFS have a reduced WR at AT in the second of two maximal effort tests which is not the case in apparently healthy controls. These findings provide some evidence of possible limitations of aerobic capacity which would appear to happen in the 24hrs following high intensity exercise in ME/CFS but not for controls. Based on these findings it would be useful to explore the lowest demand needed to produce this response and assess the feasibility of repeated exercise at lower intensities. This review provides evidence that people with ME/CFS appear to demonstrate a measurable response to high intensity exercise that is not present in apparently healthy controls. These findings add support to the hypothesis of a physiological mechanism involved with ME/CFS and may provide useful information to support diagnosis.

Summary of Chapter 6

This review provides evidence that WR at AT may be a possible discriminative marker for people with ME/CFS vs healthy controls. These findings are twofold, firstly, this may be useful in creating an objective diagnosis for ME/CFS. Secondly, if these findings are replicated, this provides evidence that people with ME/CFS demonstrated a distinct and measurable difference to high intensity exercise that is not demonstrated in apparently healthy controls. Although there are only a small number of studies in this review, if these findings can be verified then this would question the validity of the cognitive behavioural model that underpins GET. Due to the debate around the effectiveness of GET in ME/CFS an assessment of this as an intervention is an essential aspect of understanding how this may be used as a treatment.

Although these findings are useful in understanding possible mechanisms involved with ME/CFS, the ethical implications of asking people with this illness to exercise to exhaustion twice in 24 hours should not be overlooked. Alternatives that require testing at lower exercise intensities should be considered for future studies.

CHAPTER 7: The Effectiveness of Exercise Interventions in Reducing Symptoms of Fatigue in ME/CFS

7.0 Background

Chapters 5 and 6 contribute to the growing body of evidence that people with ME/CFS have an objective and measurable response to high intensity exercise that is not demonstrated in apparently healthy controls. Whilst the mechanism that underpins this is currently unknown, these findings add support to the hypothesis of a physiological component of the illness. This contradicts the cognitive behavioural/ deconditioning models of ME/CFS (Vercoulen *et al.*, 1998; Harvey and Wessely, 2009) which state that the illness is maintained primarily through psychological factors which in turn lead to inactive behaviours (Oldershaw *et al.*, 2011).

Graded exercise therapy (GET) is commonly recommended as a treatment for ME/CFS (NICE, 2007) and was developed based on the cognitive behavioural model of ME/CFS (Moss-Morris *et al.*, 2005; White *et al.*, 2011). Proponents of GET argue that it is effective as it treats the physiological deconditioning which is a key cause of the symptoms of fatigue (Clark and White, 2005). Clark and White (2005) stated that inactivity in people with ME/CFS causes a reduction in physical strength and cardiovascular endurance as well as changes in the central nervous system, known more generally as deconditioning. When people with ME/CFS are not able to function at pre-illness levels due to deconditioning this creates feelings of frustration which causes low mood, lack of motivation and lethargy (Clark and White, 2005).

This results in an increase in sedentary behaviour and a perpetuation of ME/CFS symptoms (Clark and White, 2005). Clark and White (2005) further stated that deconditioning in people with ME/CFS was a result of an abnormal perception of effort and that GET aims to modify this abnormal effort perception by encouraging patients to focus on non-symptom cues (such as heart rate and perceived exertion) while gradually increasing their activity levels.

It is proposed that by focusing on these non-symptom cues during GET, people with ME/CFS are taught to understand that body sensations are a normal response to activity and not due to an organic illness (Wilshire *et al.*, 2018). This in turn can change their negative beliefs about their symptoms (Powell *et al.*, 2001; Moss-Morris *et al.*, 2005) because a belief that ME/CFS has an organic cause reduces the likelihood of a successful outcome (Moss-Morris *et al.*, 2005). Consequently, this will reduce the enhanced perception of effort during exercise in people with ME/CFS brought on by deconditioning and improve their symptoms (Clark and White, 2005).

To date, a number of studies have reported that GET is an effective intervention in reducing symptoms of fatigue in ME/CFS (Powell *et al.*, 2001; Moss-Morris *et al.*, 2005; White *et al.*, 2011; Larun *et al.*, 2019). However, some authors are critical of the use of GET in treating ME/CFS arguing the treatment method can be harmful for some sufferers (Twisk and Maes, 2009; Geraghty and Blease, 2019) and that the methodologies of these studies are

poor and lack the degree of rigour required to make evidence-based decisions (Twisk and Maes, 2009; Geraghty and Blease, 2019). These criticisms have been supported by a number of surveys that report GET worsening symptoms in a number of people with ME/CFS (ME Association, 2015; Geraghty *et al.*, 2019a).

A Cochrane systematic review assessing exercise interventions was conducted by Larun *et al.* (2019) which reported that exercise therapy 'probably reduces fatigue' when compared to passive treatments or no treatment. This review also stated that there is uncertainty about the risk of serious adverse reactions because of a lack of evidence. Larun *et al.* (2019) meta-analysed standardised mean difference to combine studies using different fatigue scales which may introduce heterogeneity that is unrelated to any real between study difference. Instead, this could be related to factors such as different sampling methods or sampling variation (Hopkins, 2018). This review has also received substantial criticism as many believe it is inappropriate to include the RCT by White *et al.* (2011) (The PACE trial) as the risk of bias in this study is viewed by some to be substantially high (Wilshire *et al.*, 2017). Critics also argue that studies which have used the Oxford Criteria case definition (Sharpe *et al.*, 1991) should not be included as these may consist of individuals who are healthy or have other conditions of which fatigue is a symptom, however do not meet other more stringent definitions of ME/CFS (IOM, 2015).

Therefore, the aim of this review is to conduct a systematic review and meta-analyses assessing the effectiveness of exercise interventions in reducing symptoms of fatigue in people with ME/CFS. The findings will be considered in relation to a scientifically relevant threshold. The impact of removing the PACE trial and studies that utilise the Oxford diagnostic criteria will also be assessed.

7.1 Aims

The primary aim of this review is to assess the effectiveness of graded exercise interventions in reducing symptoms of fatigue in people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

The secondary aims of this review are to assess how removal of the PACE trial (White *et al.*, 2011) and the removal of studies which have used the Oxford Criteria case definition (Sharpe *et al.*, 1991) impacts on the magnitude of the pooled effect.

This review was registered in the Prospero register for Systematic Reviews (CRD42017081033)

(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=81033).

There were two changes from the original protocol. Initially the aim was to compare the mean change in fatigue (post fatigue minus pre fatigue scores) between the two groups. However, due to the unavailability of data the

decision was made to use the post data only, assuming that the randomisation process produced groups that were roughly equal at baseline in each study. This method is described in Higgins and Green (2011) as appropriate, although this may affect the precision of the results due to a reduced ability to control for between-person variability (Deeks *et al.*, 2019). Nevertheless, Deeks *et al.* (2019) stated that in randomised controlled trials the mean post-intervention values will be on average the same as the difference in mean change scores and that this is an appropriate method when conducting a meta-analysis of RCTs.

Secondly, the removal of the PACE trial and studies which use the Oxford Criteria case definition was not included in the original registration. However, based on recommendations by IOM (2015) the research team decided to include these analyses in this review. The PRISMA guidelines (Liberati *et al.*, 2009) were used in the reporting of this review.

7.2 Design

The design for this study is a systematic review of randomised controlled trials (RCTs) with meta-analyses.

7.3 Criteria for selecting studies into the review

For the purpose of this review the PICOS (Population, Intervention, Comparison, Outcome, Studies) (McKenzie *et al.*, 2019) structure was used

to provide clarity when devising the inclusion and exclusion criteria and developing the comprehensive search strategy.

The eligibility criteria for this review were:

Population: to be included in this review participants were required to have a diagnosis of ME/CFS using any recognised diagnostic definition. This included the Oxford criteria (Sharpe *et al.*, 1991), Fukuda *et al.* (1994), the Canadian Criteria (Carruthers *et al.*, 2003), the International Consensus Criteria (ICC) (Carruthers *et al.*, 2011), NICE (2007) and Komaroff *et al.* (1996). Studies were excluded if the sample included those diagnosed with chronic fatigue, chronic fatigue like illness (or symptoms) or idiopathic chronic fatigue.

Intervention: for the purpose of this review any study assessing any type of exercise or physical activity intervention was included. Specifically, this entailed any intervention that aimed to increase the amount of exercise and/or physical activity the participant undertook. Studies that included a co-intervention such as CBT or varying levels of support were included. However, studies must have stated explicitly in the title and/or abstract that exercise was used. Studies that primarily used an intervention for example CBT and incorporated an exercise element in the methods but did not discuss its use in the title and abstract were excluded. For inclusion in this review interventions could include aerobic or anaerobic exercises and group or individual programmes. Studies were also included irrespective of label, for example, GET, exercise programme, incremental exercise programme or pacing

however to be included in this review the programme was required to involve some progression in terms of frequency, intensity and/ or duration.

Comparison: Studies were required to include a comparison group, these included; relaxation, flexibility, standard treatment, specialist medical treatment, care as usual. Studies which compared GET vs. another intervention such as CBT or another form of exercise intervention were not included.

Outcome: the main outcome of interest for this review was fatigue. Any scale designed to assess fatigue in this population was included. These included: The Chalder Fatigue Questionnaire (CFQ) (Chalder *et al.*, 1993), the fatigue severity scale (FSS) (Krupp *et al.*, 1989) and the checklist individual strength (CIS) scale (Vercoulen *et al.*, 1994). If a study reported multiple fatigue scales, the CFQ was prioritised as this is the most commonly cited fatigue scale used within the ME/CFS literature. Post data was taken from the end of the intervention period and follow-up data was not analysed in this review.

Types of Studies; Studies were required to be randomised controlled trials (RCT). No other types of study were included in this review. Studies were required to be published in a peer reviewed journal. Grey literature was excluded as there may have been inadequate overview of the methods to conduct a risk of bias assessment.

7.4 Comprehensive literature search

One author (JF) conducted a comprehensive literature search of Medline, PsycINFO, CINAHL, AHMED, SPORTDiscuss, Psychology and behavioural sciences collection, PsychARTICLES and Embase from inception to January 2019. A follow-up search was conducted in January 2020 and no new papers were retrieved. The comprehensive search strategy was peer reviewed by a member of the research team and a Senior Librarian at Teesside University before the full comprehensive search was conducted. The following search terms and Boolean Operators were used:

(MH "Fatigue Syndrome, Chronic") OR myalgic encephalo* OR CFS OR ME
OR CFS/ME

AND

Graded exercise therapy OR (MH "Exercise") OR (MH "Resistance Training")
OR (MH "Therapeutic Exercise") OR (MH "Exercise Intensity") OR (MH
"Physical Activity") OR (MH "Activities of Daily Living")

AND

(MH "Fatigue") OR symptoms OR quality of life OR wellbeing OR well-being
OR well being OR manag*

For the MEDLINE database the intervention terms were modified following use of the "subject heading" searching function. The Medline modified search terms were:

Graded exercise therapy OR (MH "Exercise") OR (MH "Exercise Therapy") OR
(MH "Resistance Training") OR Physical Activity

Hand searching was conducted and previous systematic reviews (Marques *et al.*, 2015; Larun *et al.*, 2019) were checked. Searches were conducted on google scholar and reference lists of papers were checked.

7.5 Selection of studies

JF conducted both the first and second selection of studies. First selection involved assessing the titles and abstracts for eligibility. Those papers which were deemed 'yes' or 'maybe' from the first selection were assessed in the second selection process. This involved assessing the suitability for inclusion of possible papers by reading the full text. During the second selection process the three reviewers met on three separate occasions to discuss the papers. Specifically, a discussion took place around including studies that involved co-interventions, such as CBT. A previous review by Marques *et al.* (2015) had included studies that were described by the authors as CBT, however also included an exercise element. Although the authors of these papers referred to the interventions as CBT without a mention of exercise in the title and abstract. After consideration of these papers a consensus was reached to exclude them from this review. It was agreed that these studies were described by the authors as CBT interventions and not explicitly GET, and therefore for the purposes of this review it was not appropriate to view these studies as exercise interventions. Papers that explicitly stated the use of exercise in the

abstract were included. During the final meeting, all full text papers were discussed and a consensus on the final papers for inclusion was reached.

7.6 Risk of Bias

The risk of bias has been conducted in two stages. The first involved assessment using the Risk of Bias (RoB) 2.0 tool (Sterne *et al.*, 2019). The RoB 2.0 tool was conducted as described by Higgins *et al.* (2019) in chapter 8 of the Cochrane Handbook. Five domains were assessed for the risk of bias using signalling questions with five responses (yes, probably yes, probably no, no, no information). After assessment of all domains, the study is classified as either low risk of bias, some concerns or high risk of bias.

The second assessment used the Consensus on Exercise Reporting Template (CERT) checklist (Slade *et al.*, 2016). Slade *et al.* (2016) stated that the write-up of complex interventions is often poor and that the Template for Intervention Description and Replication (TIDieR) checklist has been developed to aid in assessing these (Hoffman *et al.*, 2014). However, Slade *et al.* (2016) argued that for complex exercise interventions there is specific information which should be reported such as type of exercise, dosage, intensity and frequency, and whether or not it required supervision or individualisation. To date, reviews which have been conducted on this topic have assessed quality using risk of bias assessments, however no review has conducted an explicit assessment of the exercise intervention itself.

JF conducted the quality assessments on all papers twice and checked these for consistency. Following this, a discussion took place between the three reviewers on key methodological aspects of the included papers. This process was conducted over a period of approximately 9 months (January 2019 – September 2019) during this time the full research team met regularly to discuss key aspects of the included studies. Each question on the RoB 2.0 tools was also considered and a consensus on what should be focused on to ensure consistency. For example, question 4 on the RoB 2.0 tool focused on the blinding of outcome assessors. Originally JF had assessed each paper as high risk, however following a discussion it was agreed that as the outcome was self-assessed by patients this could be assessed as ‘some concerns’ or ‘low risk’ depending on the specific information provided in each paper. It was agreed in this discussion that the ‘high risk’ rating is triggered on the study quality tool if there is an element of judgement from the observer on an outcome. However, as the outcome is a subjective scale which the participant scores themselves this would not result in a high risk of bias. Following this process, a consensus was reached on the specifics of each assessment tool. A full audit trail was kept by JF.

7.7 Data Extraction

All data was extracted on two separate occasions by JF and then checked for consistency. Information relating to the sample, diagnostic definition, intervention and comparison groups were extracted from each paper and inputted into Microsoft excel. In addition, data relating to post-fatigue scores,

number and reasons of dropouts and number of adverse events were extracted from each of the papers.

Fatigue was measured using four different instruments across the included papers (summarised in table 7.2 in the results section). As studies in this review used multiple instruments to assess the same underlying construct (fatigue) the data was converted to a common metric (percentages) to allow for comparison. Higgins and Green (2011) recommend using the standardised mean difference (SMD) to pool multiple instruments measuring the same construct. This involves dividing the mean difference between two groups by the study SD (Higgins and Green, 2011). The magnitude of treatment effects will then be presented as SD units (Johnston *et al.*, 2010). This was supported by Takeshima *et al.*, (2014) who reported the SMD was the most effective summary statistic to use as it allowed the most effective generalisability. However, Johnston *et al.*, (2010) argues a number of limitations of using SMD. Firstly, it can be difficult for clinicians and patients to interpret the magnitude of the effect of SD units. Borenstein *et al.*, (2012) supported this arguing that an important consideration of a meta-analysis is that the results are intuitively meaningful either inherently or because of widespread use.

A second criticism of the SMD is if the heterogeneity of patients differs in different studies, so will the SD (Johnston *et al.*, 2010). Therefore, trials with a more heterogeneous patient group but a similar score to a less heterogeneous patient group will show a smaller effect (Johnston *et al.*, 2010). Hopkins (2018)

supported this argument adding that, differences in the SD between studies which may reflect different populations, different methods of sampling, or just sampling variation will introduce heterogeneity that is unrelated to any real differences in the treatment effect. Hopkins (2018) argues that the most effective method to combine studies using multiple tools measuring the same construct is to convert the data to percentages. Due to these limitations of SMD all fatigue data was extracted and converted to a percentage.

To enable pairwise comparisons from each of the papers (Higgins and Green, 2011) where a study included more than two groups, these were either combined, or data was only taken from two groups and the other groups excluded. Table 7.2 provides an overview of this process and the data that was included in the meta-analysis. Means and standard deviations were combined using the method described by Higgins and Green (2011) (section 7.7.3.8). When data was presented as a 95% confidence interval, the SD was obtained by first converting the 95%CI into a SE (width of CI divided by $2 \times t$ -value for the degree of freedom and $p=0.975$) and then converting the SE to a SD. The order of conversion was 1) convert any 95%CIs to SDs 2) combine means and SDs 3) convert to percentages. The calculations were completed by JF on two separate occasions and then compared for accuracy. For most studies there was no inconsistencies in the statistics that were generated with the exception of Powell *et al.* (2001). Powell *et al.*'s (2001) study required all the conversion stages above and large discrepancies in the pooled SDs was noted between the two sets of data. When assessing where this error occurred, there was ambiguity in the way the paper reported the sample sizes

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in each group which resulted in two different sample sizes being used. To ensure accuracy, these were calculated a further two times and this discrepancy was highlighted to the research team. After this process, the statistics generated on the first occasion were found to be correct.

Table 7.1; Researchers contacted during data extraction

Study Researcher (Email)	Information requested	Response
Larun <i>et al.</i> (2019) Lillebeth Larun lillebeth.larun@kunnskapssenteret.no	Queried statistics reported in meta-analysis in relation to Wallman <i>et al.</i> (2004) that did not match original paper	Discussion via email however unclear why this difference had occurred
Wallman <i>et al.</i> (2004) Karen Wallman karen.wallman@uwa.edu.au	Queried statistics reported in meta-analysis in Larun <i>et al.</i> (2019) and how these did not match the data in the original publication.	Discussed via email. Original dataset had been passed on to Cochrane group.
Chalder <i>et al.</i> (XX) Professor Trudie Chalder trudie.chalder@kcl.ac.uk	Queried if an MCID had been established for the CFQ	No response
Kos <i>et al.</i> (2015) Dr Daphne Kos daphne.kos@kuleuven.be	Requested post treatment data for the ME/CFS and control groups mean and SD for total CIS score	All data requested was provided

CFQ – chalder fatigue questionnaire

7.8 Data analysis

Data was inputted into Comprehensive Meta-Analysis Software (CMA) version 3, in duplicate for analysis. A random effects meta-analysis was conducted using the DerSimonian and Laird (method of moments) estimator with t-distribution (Knapp and Hartung) to assess heterogeneity.

To determine the MCID for fatigue the Cochrane review by Larun *et al.* (2019) was referred to which used an MCID threshold of 7% (2.3pts on 11-item CFQ) taken from Goligher *et al.* (2008) (see table 7.1). To verify this threshold, a literature search was conducted which found MCID threshold for the CFQ, FSS and CIS scales in systemic lupus erythematosus (Goligher *et al.*, 2008) and rheumatoid arthritis (Pouchot *et al.*, 2008) and two studies in multiple sclerosis (Robinson *et al.*, 2009; Rietberg *et al.*, 2010). This information was also summarised in a systematic review by Nordin *et al.* (2016). The MCIDs for the CFQ, FSS and CIS scales are summarised in table 7.1. Based on this data the MCID threshold used in Larun *et al.* (2019) appeared to be the lowest of all the MCIDs identified and only relevant to the CFQ. Therefore a decision was made to use the more conservative estimate of 10% for the MCID for the change in fatigue as this threshold took into account the other fatigue scales. However, in the absence of any other data this MCID threshold should be considered an estimation only, and it is acknowledged that this as a limitation of our analysis.

Table 7.2; MCID values reported for FSS, CFQ and CIS

Study (population) (sample size)	Fatigue Severity Scale (FSS) % (95% CI)	Chalder Fatigue Questionnaire (CFQ) (11-item; 0-33) % (95% CI)	Checklist Individual Strength (CIS) (20-item) % (95% CI)
Rooney <i>et al.</i> , (2019) (Multiple sclerosis) (n=365)	6.4 - 12.6%	Did not assess	Did not assess
Rietberg <i>et al.</i> , (2010) (Multiple Sclerosis) (n=43)	20.8%	Did not assess	17.7%
Robinson <i>et al.</i> , (2009) (Multiple Sclerosis) (n=249)	8 - 18%	Did not assess	Did not assess
Goligher <i>et al.</i> , (2008) (Systemic Lupus Erythematosus) (n=80)	9.7% (4.9 to 14.6)	7% (2.9 to 11.1)	Did not assess
Pouchot <i>et al.</i> , (2008) (Rheumatoid Arthritis) (n=61)	20.2% (15.5 to 25)	9.9% (5.9 to 13.8)	Did not assess

Two further meta-analyses were conducted. The second meta-analysis was conducted removing the PACE trial (White *et al.*, 2011) and the third analysis was conducted following removal of studies that used the Oxford Criteria. The PACE trial has received substantial criticism in the literature and in 2018 an open letter was written to the Lancet by 100 academics, patient groups, lawyers and politicians requesting an investigation into the study due to

significant methodological weaknesses (Torjesen, 2018). Therefore, the aim was to assess the impact of removing this study on the overall pooled effect.

There is growing evidence that the Oxford Criteria for ME/CFS may lack sensitivity and specificity, including healthy subjects as well as those with milder fatigue which would not meet the criteria of other definitions. Some have argued that findings from studies that use the Oxford Criteria case definition should be viewed sceptically (Baraniuk, 2017). The IOM (2015) also recommended retiring this case definition and therefore we aim to assess the impact of removing these studies.

A prediction interval was calculated to provide a range of the likely effects in a future study conducted in similar settings (IntHout *et al.*, 2016). Using the methods described by Mathur and VanderWeele (2018) the proportion of future studies conducted in a similar setting that would exceed the MCID for the difference in fatigue was calculated.

7.9 Results

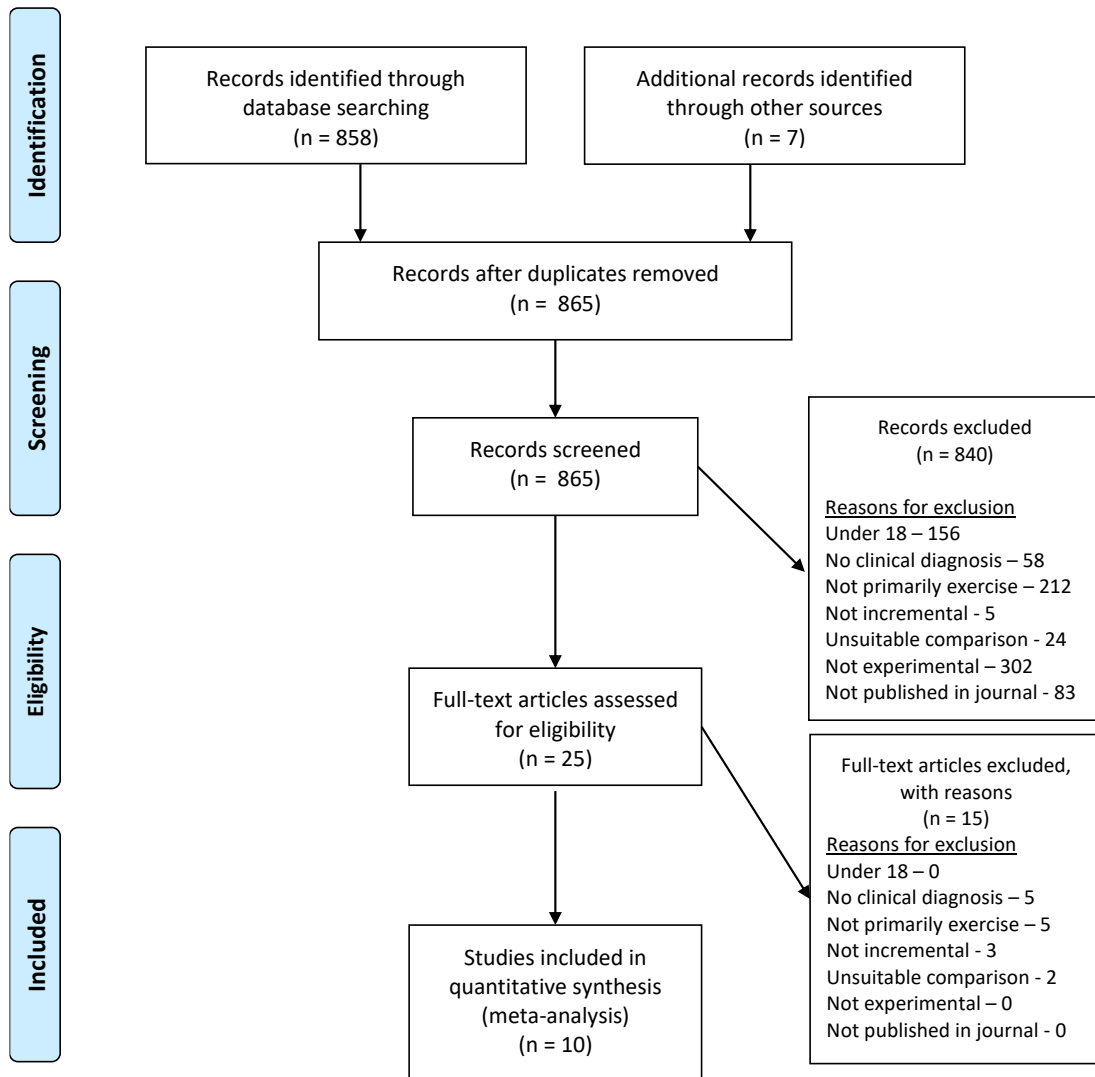
7.9.1 Results of Literature Search, 1st and 2nd Selection

Combined searches resulted in 865 titles and abstracts being assessed for inclusion into the review. Following 1st selection, the number of studies reduced to 25 and this was reduced to 10 studies following the 2nd selection process. A summary of the study selection process can be seen in figure 7.1.

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Two studies (Wallman *et al.*, 2004; White *et al.*, 2011) were discussed in detail and the decision relating to these specific papers is noted below.

Figure 7.1; PRISMA flow diagram of study selection



7.9.1.1 Studies of note

There were two studies of note that were believed to require an explicit justification for why they were included or excluded. The two studies of note are White *et al.* (2011) and Wallman *et al.* (2004).

7.9.1.2 White *et al.* (2011) (The PACE trial) – included

White *et al.* (2011) has come under considerable criticism in the literature. Critics argue that substantial changes in the outcome measures from the original protocol were made and that the study recruited participants who had already met the trial's threshold for 'recovered' before the commencement of the trial resulting in an unacceptably high risk of bias (Vink and Vink-Niese, 2018; Wilshire *et al.*, 2018). However, as this study met the inclusion criteria it was included nevertheless. The impact of removing this study from the analysis is investigated.

7.9.1.3 Wallman *et al.* (2004) – excluded

A discrepancy was noted when extracting data from Wallman *et al.* (2004) and comparing against a previous meta-analysis (Larun *et al.*, 2019). In Wallman *et al.* (2004), the total fatigue score for the exercise group and the relaxation/ flexibility was 12.6 and 14.4 respectively, resulting in a mean difference of - 1.8. In the paper by Larun *et al.*, (2019), the post data for the exercise group and relaxation/ flexibility group was 11.06 and 15.34 respectively providing a mean difference of -4.28. This resulted in a larger effect in the meta-analysis

by Larun *et al.*, (2019) than was reported in the original paper (Wallman *et al.*, 2004) (13% reduction in fatigue vs. 5.5%). Both research groups were contacted, however the Wallman research group no longer had the original data and this discrepancy was unable to be clarified with the Larun research group. Due to this inconsistency, the decision was made to exclude this paper from the analysis.

7.9.2 Overview of Included Studies

Tables 7.2 and 7.3 provide a summary of the included papers. The 10 included papers are all RCTs, 4 studies used the Fukuda *et al.*, (1994) case definition, 5 studies used the Oxford Criteria case definition and 1 study used NICE (2007) case definition. The length of the interventions varied between 3 weeks and 12 months with 6 studies lasting 12 weeks (or 3 months). Four different fatigue scales were used; 2 studies used the FSS (Jason *et al.*, 2007; Broadbent and Coutts, 2016), 1 study used the CIS (Kos *et al.*, 2015), 3 studies used the 14-item CFQ using a 4pt Likert Scale (Fulcher and White, 1997; Wearden *et al.*, 1998; Moss-Morris *et al.*, 2005), 2 studies used the 11-item CFQ using the binary scoring system (Powell *et al.*, 2001; Wearden *et al.*, 2010) and 2 used the 11-item CFQ using the 4pt Likert Scale (White *et al.*, 2011; Clark *et al.*, 2017;). Eight studies provided information relating to psychiatric comorbidities. The proportion of the sample having some form of pre-existing psychiatric disorder, either as taking anti-depressants or having a diagnosis ranged from 9% (Clark *et al.*, 2017) to 62% (Jason *et al.*, 2007). Proportion of pre-existing psychiatric disorder was 56% (Moss-Morris *et al.*,

2005), 41% (Fulcher and White, 1997), 18% (Powell *et al.*, 2001), ~40% (White *et al.*, 2011), ~25% (Wearden *et al.*, 2010) and 46% (Wearden *et al.*, 1998).

Seven studies compared against standard medical, specialist medical care or usual treatment. Three studies compared against a flexibility or relaxation. One study (Broadbent and Coutts, 2016) used a lab-based intervention relating to participants VO_{2peak} .

The aim of three of the interventions was to achieve 30 minutes of exercise 5 days per week (or 3 days per week in Wearden *et al.*, 1998) at 70% VO_{2peak} (Moss-Morris *et al.*, 2005), 60% VO_{2peak} (Fulcher and White, 1997), or 70% of functional capacity (defined as peak VO_2 at termination of maximal exercise test when peak not achieved) (Wearden *et al.*, 1998). Frequency of exercise was not reported in Broadbent and Coutts (2016), Powell *et al.* (2001), Jason *et al.*, (2007) and Clark *et al.* (2017). The reporting of the intervention lacked detail in 3 studies (Powell *et al.*, 2001; Jason *et al.*, 2007; Kos *et al.*, 2017). One study (Broadbent and Coutts, 2016) was lab based which required participants to use a cycle ergometer. The remaining 9 studies negotiated the type of activity with each participant, 2 studies (Fulcher and White, 1997; Clark *et al.*, 2017) reported that walking was the most common form of exercise however encouraged other forms of aerobic exercise.

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Table 7.3; Overview of study characteristics

Study	CFS/ME diagnostic definition	Sample size Total Treatment: comparison	Duration of intervention	Fatigue scale used	Conversions conducted on data for meta-analysis	Data inputted into meta-analysis (%) Mean (SD)	% difference between intervention and comparison	Proportion of included sample with diagnosed psychiatric disorder
Broadbent and Coutts (2016)	Fukuda <i>et al.</i> , (1994) and CDC (2011)	24 16:8	12 weeks	Fatigue Severity Scale (FSS) 9 questions on 1-7 Likert scale Max=9, min=63 Data reported as mean of total score (1-7)	Results reported as % Combined GE and IE means, and SDs Data converted into % (value*9-9/54*100)	Intervention group = 78.6 (16.4) Comparison group = 87.5 (10.1)	8.9% in favour of intervention MCID for FSS = 8% to 20.2%	Unknown
Moss-Morris <i>et al.</i> , (2005)	Fukuda <i>et al.</i> , (1994)	49 25:24	12 weeks	Chalder Fatigue Scale 14 questions on a 0-3 Likert scale	Pre and post mean and SD provided. Data converted in % (value over 42*100)	Intervention group = 33.1 (25.9) Comparison group = 58.1 (23.1)	25% in favour of intervention MCID for CFQ (14-item) = unknown	56% 30% possible or probable cases of depression - 13% probable.

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				Max=42, min=0				42% possible or probable cases of anxiety disorder – 13% probable.
Fulcher and White (1997)	Oxford Criteria	66 33:33	12 weeks	Chalder Fatigue Scale 14 questions on a 0-3 Likert scale Max=42, min=0	Pre and post mean and SD provided. Data converted in % (value over 42*100)	Intervention group = 48.8 (21.2) Comparison group = 65.2 (17.6)	16.4% in favour of intervention MCID for CFQ (14- item) = unknown	27 (41%) had been treated for a comorbid disorder beforehand but still met criteria 20 patients were talking antidepressants
Powell <i>et al.</i> , (2001)	Oxford Criteria and <25 on physical functioning subscale of SF-36	148 114: 34	3 months	Chalder Fatigue Scale 11 questions with binary response (0 or 1) Max=11, min=0	3 groups combined for intervention group (minimum, telephone and maximum intervention) 95%CI converted to SD Means and SDs combined	Intervention group = 39.1 (41.4) Comparison group = 94.5 (9.1)	55.4% in favour of intervention MCID for CFQ (11- item – binary response) = unknown	18% of total sample taking antidepressants

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					Data converted to % (value over 11*100)			
White <i>et al.</i> , (2011)	Oxford criteria and	316 159:157	24 weeks	Chalder Fatigue Scale	Pre and post mean and SD provided.	Intervention group = 65.8 (21.5)	6.9% in favour of intervention	74 (46%) and 66 (41%) taking antidepressants at baseline and 61 (40%) and 60 (39%) in the GET and SMC groups respectively.
				11 questions on a 0-3 Likert scale	Data extracted from GET and SMC groups only	Comparison group = 72.7 (20.9)	MCID for CFQ (11-item) = 7% to 9.9%*	
				Max=33, min=0	Data converted in % (value over 33*100)			
Wearden <i>et al.</i> , (2010)	Oxford criteria and scored ≤ 70% on SF-36 and ≥ 4 on CFQ**	177 85:92	18 weeks	Chalder Fatigue Scale	Pre and post mean and SD provided.	Intervention group = 76.3 (33.4)	8.4% in favour of intervention	Any anxiety diagnosis 26.6% treatment group 25.6% in the control
				11 questions with binary response (0 or 1)	Data extracted from pragmatic rehabilitation and general practitioner groups only	Comparison group = 84.7 (28.9)	MCID for CFQ (11-item – binary response) = unknown	Any depression diagnosis 18.9% in the treatment group 20% in the control group
				Max=11, min=0	Data converted in % (value over 11*100)			
Wearden <i>et al.</i> , (1998)	Oxford criteria	68 34:34	26 weeks	Chalder Fatigue Scale	Data taken from two groups only.	Intervention group = 66.7 (25.92)	7.8% in favour of intervention	62 subjects (46%) had a current

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				14 questions on a 0-3 Likert scale Max=42, min=0	Exercise and placebo (intervention), exercise control and placebo (control). Data reported as mean change and 95% CI. 95%CI converted to SD Data converted in % (value over 42*100)	Comparison group = 74.5 (18.5)	MCID for CFQ (14 item) = unknown	psychiatric disorder; 14 (10%) had major depression, 32 (24%) had either dysthymia or depressive disorder, 14 (10%) had anxiety disorders, 2 (2%) had somatisation disorder.
Jason <i>et al.</i> , (2007)	Fukuda <i>et al.</i> , (1994) and Komaroff <i>et al.</i> , (1996)	57 29:28	12 months	Fatigue Severity Scale (FSS) 9 questions on 1-7 Likert scale Max=9, min=63	Pre and post mean and SD provided. Data extracted from the anaerobic activity therapy group (treatment) and the relax group (control)	Intervention group = 79.5 (7.2) Comparison group = 77 (1)	-2.5% in favour of control MCID for FSS = 8% to 20.2%	62.3% had a lifetime Axis I diagnosis. 38.6% had a current Axis I diagnosis (depressive and anxiety disorders reported as most common)

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				Data reported as mean of total score (1-7)	Data converted into % (value*9-9/54 *100)			
Clark <i>et al.</i> , (2017)	NICE criteria, CDC criteria (2003) and Oxford criteria*	211 107:104	12 weeks	Chalder Fatigue Scale 11 questions on a 0-3 Likert scale Max=33, min=0	Pre and post mean and SD provided. Data extracted from GES and SMC groups Data converted in % (value over 33*100)	Intervention group = 57.9 (23) Comparison group = 69.4 (20.9)	11.5% in favour of intervention MCID for CFQ (11-item) = 7% to 9.9%	Current major depressive disorder – 10(9%) in GES group, 11(11%) in SMC group.
Kos <i>et al.</i> , (2015)	Fukuda <i>et al.</i> , (1994)	26 12:14	3 weeks	Checklist individual strength (CIS) 20 questions on a 1-7 Likert scale Max=140 Min=20	Data reported in paper as median and IQR. Author's contacted for data.	Intervention group = 66.4 (8.1) Comparison group = 75.1 (10.2)	8.7% in favour of intervention MCID for CIS (20-item) = 17.7%	Not reported

*Not clear if all diagnostic criteria had to be met or if this data was collected for information only. CDC – Centre for Disease Control and Prevention. SMC – specialist medical care. GES – graded exercise self-help.

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Table 7.4; overview of intervention and comparison groups

Study	Intervention	Comparison	Results (as presented in study)
Broadbent and Coutts (2016)	<p>All exercise on spin cycle ergometer. 12-week programme.</p> <p>Either intermittent exercise (IE) involving 5mins warm-up, 10-15mins of 1min moderate exercise (60% VO_{2peak}) 1min unloaded at 50-70rpm.</p> <p>Or graded exercise (GE) involving 5mins warm-up, 10-15mins 50%VO_{2peak} at 50-70rpm.</p> <p>Progressed by duration first. Once 3x30min sessions completed load increased by 10% of current workload.</p> <p>Frequency of sessions not reported</p>	Usual care (UC) - asked to follow advice of medical practitioner and not to engage in any other physical activity during study.	<p>Post intervention fatigue score reported as %mean and SD</p> <p>GE – 84.1±14.1% IE – 73.1±17.6% UC – 87.5±10.1%</p> <p>(P = 0.75)</p>
Moss-Morris <i>et al.</i> (2005)	<p>Initial meeting for one hour to discuss programme and theory. Individual plan, started at 50% age predicted max (40% of VO_{2peak}) for 10-15mins, 4-5 times a week. Heart rate used to focus on during programme. Researcher and participant met weekly to set goals. Progression on increasing duration for initial 6 weeks, then increase in HR by 5bpm/ week. Goal for each participant to exercise 30mins, 5times per week at 80% predicted HR max (70% VO_{2peak}).</p>	Standard medical care	<p>Post intervention fatigue scores reported as mean and SD</p> <p>Treatment = 13.91±10.88</p> <p>Control = 24.41±9.69</p> <p>(P = 0.02)</p>

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Fulcher and White (1997)	<p>Attended weekly for supervised session and plan for following week. 1 laboratory session per week, five home sessions per week. Sessions initially lasted between 5-15mins at 40% predicted maximum heart rate (40% of VO_{2peak}). Duration increased by 1-2mins until reached 30mins. Workload then increased to a maximum of 60% of VO_{2peak}. Heart monitors used throughout. Patients asked to walk however encouraged to cycle and walk.</p>	<p>Flexibility. Attended weekly for flexibility and relaxation sessions. Initially 10mins, progressed to 30mins 5 days per week. Asked not to participate in an extra physical activity.</p>	<p>Post intervention fatigue scores reported as mean and SD</p> <p>Treatment = 20.5 ± 8.9</p> <p>Control = 27.4 ± 7.4</p> <p>($P = 0.004$)</p>
Powell <i>et al.</i> (2001)	<p>All groups given an assessment and the explanation of their symptoms which encouraged graded exercise. Alongside this, participants were in one of three groups.</p> <p>Minimum intervention – two face to face sessions (3 h total) symptoms explained and programme designed.</p> <p>Telephone intervention – minimum intervention plus seven planned telephone calls each lasting 30mins. Reiterated programme and discussed problems relating to exercise programme.</p> <p>Maximum intervention – as minimum intervention however received seven face to face sessions.</p>	<p>Standardised medical care. Included a medical assessment, advice and information booklet that encouraged graded exercise and positive thinking.</p>	<p>Post intervention fatigue scores reported as mean and 95%CI</p> <p>Minimum intervention = 5.0 (3.4 to 6.6)</p> <p>Telephone intervention = 3.7 (2.3 to 5.2)</p> <p>Maximum intervention = 4.3 (2.9 to 5.8)</p> <p>Control = 10.4 (10.1 to 10.8)</p>
White <i>et al.</i> (2011)	<p>Intervention lasted for 24 weeks (24 weeks data taken)</p>	<p>Specialist medical care provided by doctors. Patients provided with leaflet about</p>	<p>Post intervention fatigue scores</p>

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	Individual therapy supervision was provided every month and by group every three months. Baseline established by assessing an achievable level of exercise or physical activity. Negotiated incremental increases with the aim of 30mins exercise 5 days/ week. At this point intensity increased.	CFS/ME and general advice about avoiding extremes of exercise and rest.	reported as mean and SD Treatment = 21.7±7.1 Control = 24±6.9
Wearden <i>et al.</i> (2010)	10 sessions over 18 weeks. 90min home visit week 1, 60min home visit weeks 2, 4, 10 and 19. 30min phone conversation weeks 3, 6, 8, 12 and 15. Pragmatic rehabilitation was described as a programme of graded return to activity designed collaboratively with patient and therapist.	Standard care by general practitioner.	Post intervention fatigue scores reported as mean and SD Treatment = 8.39±3.637 Control = 9.32±3.18
Wearden <i>et al.</i> (1998)	All participants attended hospital on eight occasions. Weeks 0,1,2,4,8,12,20 and 26. GET: carry out preferred aerobic exercise (walking, jogging, swimming) for 20mins 3times/wk. Initial intensity at 70% of functional work capacity (as peak oxygen uptake was not obtained, peak capacity was measured as the intensity during final minute of pre-test). Exercise progressed when HR reduced by 10bpm and 2-point reduction in post exercise RPE.	Exercise control group. No specific advice given however told to exercise and rest as they wanted. Activity diary kept by all participants in all groups.	Post intervention fatigue scores reported as mean and SD Treatment = 28 95%CI (-9.5 to -1.9) Control = 31.3 95%CI (-5.4 to 0.01)
Jason <i>et al.</i> (2007)	Anaerobic Activity Therapy (ACT). Focused on developing individualised, constructive and pleasurable activities along with	Relaxation Treatment (RELAX). Study explained and fatigue/ anxiety diary kept. Taught muscle relaxation techniques.	Post intervention fatigue scores

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	progression. Sessions 1-3 provide a rationale, including engagement and education, exercise prescription and monitoring, maintaining gains. Participants asked to gradually increase anaerobic activity levels. Sessions 4-7 – diaries reviewed goals assessed and individualised programme were provided with images for at home component. Frequency 3 times per week. Sessions 8-13 homework reviewed new targets set. Strategies for preventing and dealing with setbacks were discussed.	Asked to participate in relaxation 2 times per day for 2 weeks. At sessions 4-8 diaries reviewed. At sessions 9-13 yoga was introduced.	reported as mean and SD Treatment = 5.77 ± 1.43 Control = 5.62 ± 1.06
Clark <i>et al.</i> (2017)	Guided graded exercise self-help (GES). In addition to SMC participants provided with self-help booklet describing six steps programme of graded exercise self-help management. Six steps included, stabilising a daily routine, starting regular stretching, setting physical activity goal, choosing type of activity, setting physical activity baseline, increasing duration and intensity of activity. Most commonly chosen activity was walking. Participants had an initial meeting followed by up to three further meetings. During sessions progress was discussed and feedback and encourage was provided to increase motivation and self-efficacy. Plus, how to deal with setbacks.	Specialist Medical Care (SMC). Could involve prescription or advice regarding medication, as indicated for symptoms or co-morbid conditions such as insomnia, pain, depressive illness.	Post intervention fatigue scores reported as mean and SD Treatment = 19.1 ± 7.6 Control = 22.9 ± 6.9 ($P < 0.0001$)
Kos <i>et al.</i> (2015)	Three individual therapy sessions 60-90mins/wk for three weeks. Stabilisation phase: participants coached on how to stay within their capacity for daily	Relaxation therapy Participants provided with education about stress and ME/CFS biology and stress	Post intervention fatigue scores reported as mean and SD

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	<p>living. Provided education in the form of a booklet about fatigue and pacing. Participants asked to keep a diary.</p> <p>Grading phase: activity and exercise levels increased. Individual goals set and reflected upon in the following session.</p>	<p>management. Relaxation techniques taught and participants kept a diary.</p>	<p>Treatment = 93 ± 11.3</p> <p>Control = 105 ± 14.2</p>
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7.9.3 Overview of Risk of Bias Assessment

Tables 7.4 and 7.5 provide an overview of the risk of bias assessment. Three of the included studies were deemed to have a high risk of bias (White *et al.*, 2011; Jason *et al.*, 2007; Kos *et al.*, 2015). White *et al.* (2011) was deemed to have a high risk of bias as the study used two different measurements of fatigue but only reported one. In the study the authors report that they had originally intended to use the 0 to 11 (bimodal scoring CFQ-11item) however mid-way through the trial changed to the 0 to 33 (Likert scoring CFQ-11item) however only report the 0 to 33 score for fatigue in the 2011 paper. Due to following statement in the RoB 2.0 guidance this study was classified as high risk *'If multiple measurements were made, but only one or a subset is reported on the basis of the results (e.g. statistical significance), there is a high risk of bias in the fully reported result.'*

Jason *et al.* (2007) and Kos *et al.* (2015) were deemed as high risk as there is no information in relation to ensuring participants are analysed in the group in which they were allocated to and there is potential for this to impact on estimated effect. Jason *et al.* (2007) did not report any intention-to-treat analysis and as there is no information provided in the study this was deemed high risk (questions 2.5 and 2.6 (assignment to intervention) RoB 2.0 tool). Kos *et al.* (2015) stated that as dropout rates are the same in both groups and no participant reported initiating any other treatments no intention-to-treat analysis was conducted.

All 10 studies were scored as 'some concerns' in relation to the measurement of the outcome and this was because the fatigue outcome was completed by those who had knowledge of which group participants were allocated to (patient-reported fatigue). Broadbent and Coutts (2016) and Clark *et al.* (2017) were both scored as 'low risk'.

Scores for the CERT checklist ranged from 3 (Powell *et al.*, 2001) out of 19 to 12 out of 19 (Broadbent and Coutts, 2016). Of note, none of the included studies provided sufficient information to enable replication of the exercises with all studies scoring zero for this question. Fidelity was only measured in 3 studies (Jason *et al.*, 2007; Wearden *et al.*, 2010; White *et al.*, 2011). The methods to assess adherence was reported in 5 studies (Wearden *et al.*, 1998; Jason *et al.*, 2007; Kos *et al.*, 2015; Broadbent and Coutts, 2016; Clark *et al.*, 2017) and adverse events were reported in 4 studies (Moss-Morris *et al.*, 2005; White *et al.*, 2011; Broadbent and Coutts, 2016; Clark *et al.*, 2017). The decision rule for progression was reported in 4 studies (Fulcher and White, 1997; Wearden *et al.*, 1998; Moss-Morris *et al.*, 2005; Broadbent and Coutts, 2016). One study scored a 1 for the question 'detailed description of the exercise intervention' (Broadbent and Coutts, 2016). Eight studies received a total score of less than 10 (9.5 being half of total score). Three studies (Powell *et al.* 2001 (3); Fulcher and White, 1997 (5); Wearden *et al.*, 1998 (4)) received a score ≤ 5 , or a quarter of the total score available.

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Table 7.5: Summary of the Risk of Bias Assessment

Study 1	Randomisation process	Assignment to intervention	Starting and adhering to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Broadbent and Coutts (2016)	Low risk	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk
Moss-Morris <i>et al.</i> (2005)	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
Fulcher and White (1997)	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
White <i>et al.</i> (2011)	Low risk	Low risk	Low risk	Some concerns	Some concerns	High risk	High risk
Wearden <i>et al.</i> (2010)	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Wearden <i>et al.</i> (1998)	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
Jason <i>et al.</i> (2007)	Some concerns	High risk	Some concerns	Low risk	Some concerns	Low risk	High risk
Clark <i>et al.</i> (2017)	Low risk	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk
Kos <i>et al.</i> (2015)	Low risk	High risk	Some concerns	Low risk	Some concerns	Low risk	High risk

Table 7.6: Summary of CERT Quality Assessment

Study	Type of Equipment	Qualifications/ expertise/ training	Individual or group	Supervised or unsupervised	How is adherence measured and reported	Motivational strategies	Decision rule for exercise progression	Description of how exercise was progressed	Detailed description of exercise for replication	Description of home element	Describe any non-exercise component	Describe type and number of adverse events	Description of setting	Description of the exercise intervention	Generic or tailored	How is exercise tailored	Decision rule for starting level	How is fidelity assessed/ measured	Delivered as planned	Total score (max score 19)
Broadbent and Coutts (2016)	1	1	0	1	1	0	1	1	0	1	0	1	0	1	1	0	1	0	1	12
Moss-Morris <i>et al.</i> (2005)	0	0	0	0	0	1	1	1	0	0	1	0	0	0	1	0	1	0	0	6
Fulcher and White (1997)	0	0	0	1	0	0	1	1	0	1	0	0	0	0	0	0	1	0	0	5
Powell <i>et al.</i> (2001)	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	3
White <i>et al.</i> (2011)	0	1	1	0	0	0	0	1	0	0	1	1	1	0	1	0	0	1	1	8

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Wearden <i>et al.</i> (2010)	0	1	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	1	1	7
Wearden <i>et al.</i> (1998)	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	4
Jason <i>et al.</i> (2007)	0	1	0	1	1	1	0	1	0	0	1	0	0	0	1	0	0	1	1	9
Clark <i>et al.</i> (2017)	0	1	0	1	1	1	0	0	0	1	1	1	1	0	1	0	0	0	1	11
Kos <i>et al.</i> (2015)	0	1	1	1	1	1	0	0	0	0	1	0	0	0	1	1	1	0	0	9

7.9.4 Results of Data Synthesis

Results of the meta-analyses are summarised in table 7.7. The pooled percentage difference for the overall effect (n=10) was -13.4% (95%CI -24.2 to -2.6) in favour of intervention. Indicating that exercise results in a clinically relevant reduction in fatigue. Tau was 10.9, the 95% prediction interval (PI) (-40.3 to 13.6). The proportion of future studies which would report findings which exceed the clinically relevant threshold is 62%, 95%CI(28% to 96%).

When the PACE trial was removed from the analysis the percentage difference between treatment and control increased to 14.5% (95%CI -26.8 to -2.2), tau=12.7, 95%PI (-46.3 to 17.3) in favour of treatment. The proportion of future studies that has been estimated would exceed the clinically relevant threshold is 64%, 95%CI(31% to 96%). When studies using the Oxford case definition were removed from the analysis (n=5) the percentage difference reduced to 9% (95%CI -21.8 to -3.7), tau=9.2, 95%PI (-37.5 to 19.5) in favour of treatment. This indicates that exercise does not result in a clinically relevant reduction in fatigue. Based on the third meta-analysis the proportion of future studies conducted in a similar setting that is estimated would exceed the clinically relevant threshold of 10% is 46%, however there is substantial uncertainty with this estimate, (95%CI 7% to 85%).

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Table 7.7; Results of meta-analyses

Type of analysis	Number of included studies	Pooled effect (%)	95% CI	SE	Tau Tau ²	SE of Tau	95%PI
Overall	10	-13.4	-24.2 to -2.6	4.76	10.92 119.22	87.91	-40.35 to 13.55
PACE trial removed	9	-14.5	-26.8 to -2.2	5.35	12.71 161.58	123.96	-46.3 to 17.3
Studies using Oxford Criteria removed	5	-9	-21.8 to -3.7	4.58	9.19 84.37	85.5	-37.5 to 19.5

For the pooled effect (%) negative values favour treatment, positive values favour control. MCID for all analyses was 10%.

Table 7.8 provides a summary of adverse events and dropout rate for each included studies. Number of adverse events was described in 5 studies, however only 3 papers provided specific detail of the occurrence and type of adverse events with White *et al.* (2011) and Clark *et al.* (2017) providing the most detail. Of the studies that reported adverse events all stated that GET did not result in an increased number of adverse events. Although Moss-Morris *et al.* (2005) reported that nearly half of participants refused to take part in second VO_{2peak} test as they perceived this test to be harmful. No specific data is provided in relation to this. Three studies reported higher dropouts in the intervention group compared the control group (Wearden *et al.*, 1998; Powell *et al.*, 2001; Clark *et al.*, 2017). Kos *et al.* (2016) was the only study which did not provide any information in relation to drop out rates.

Table 7.8; Study attrition rate and number and type of adverse events

Study	Intervention drop-out rate and reasons for drop out	Number and type of adverse events
Broadbent and Coutts (2016)	2 (25%) from GE group for time constraints. 1 (12.5%) from UC group.	3 participants reported fatigue, joint pain or illness that affected their ability to exercise over the 12 weeks, for an average of 2 d. Reported that this was due to life stressors and not exercise.
Moss-Morris <i>et al.</i> (2005)	12% (3 out of 25) in intervention group 1 returned to country of origin 1 injured 1 non contactable 12.5% (3 out of 24) in control group	Not explicitly reported however study reports that nearly half of the sample refused to participate in 2 nd VO ₂ peak tests as it had been harmful – specific information has not been provided.
Fulcher and White (1997)	States in discussion 'low dropout rates...' No data on dropout rates provided.	States in discussion 'minimal adverse effect' no data provided to support this
Powell <i>et al.</i> (2001)	14% (21 participants) dropped out. 19 from intervention groups. 8 for medical reasons, 7 for psychiatric reasons, 4 give no reason, 1 emigrated, 1 dissatisfied with treatment. 6% (2 participants) dropped out of control group.	None reported
White <i>et al.</i> (2011)	GET – 1 lost to follow-up, 5 withdrew. SMC 4 lost to follow up, 4 withdrew. Reasons for participants withdrawing not provided.	Participants with non-serious adverse events GET, 149 (93%), SMC, 149 (93%). Participants with severe adverse events GET, 13 (8%), SMC 7 (4%). Difference between GET and SMC for no. of adverse events (p=0.0433). Participants with severe adverse reactions GET 2 (1%), SMC 2(1%). Serious

		deterioration GET 10 (6%), SMC (9%).
Wearden <i>et al.</i> (2010)	11% (10 participants) dropped out from intervention group. 5 declined, 4 no response, 1 researcher safety concerns. 8% (8 participants) dropped out from control group. 5 declined, 2 no response, 1 patient admitted to hospital.	None reported in relation to the intervention
Wearden <i>et al.</i> (1998)	Dropout rate higher in exercise group (25/68 (37%)) vs. non exercise group 15/69 (22%). 16 dropped out because they were not improving or feeling worse, 13 give other reasons or no reason.	None reported
Jason <i>et al.</i> (2007)	The average dropout rate was 25% with no significant differences between groups (defined as attending 4 or less sessions).	None reported
Clark <i>et al.</i> (2017)	2 lost to follow-up in SMC group. 10 lost to follow-up in GES group.	Participants reporting non-serious adverse events GES 27 (28%), SMC 23 (23%). Serious adverse events GES 1(1%) SMC 2(2%). Serious deterioration GES 20 (21%) SMC 30(30%).
Kos <i>et al.</i> (2015)	None reported	None reported

7.10 Discussion

The aim of this review was to conduct three meta-analyses. The first; all studies that met the inclusion criteria, the second with removal of the PACE trial. The third removal of all studies which used the Oxford Criteria case

definition. Results from the first meta-analysis support the hypothesis that exercise interventions are effective in reducing symptoms of fatigue in people with ME/CFS and this is in agreement with the findings of Larun *et al.* (2019). The reduction in fatigue of 13.4% was clinically relevant although there were large between study variability demonstrated by tau. The prediction interval was also large indicating a large degree of uncertainty with a possible greater improvement in the treatment group (-40%) to a possible improvement in the control group (14%).

Removal of the PACE trial resulted in a larger pooled effect in favour of the treatment. This is due to the difference in the PACE trial between treatment and control of -6.9% in favour of treatment, which was the second lowest effect of the included studies. Therefore, exclusion of this study from the second meta-analysis resulted in a greater overall pooled effect in favour of treatment. Removal of studies that applied the Oxford Criteria resulted in a reduction in the pooled effect to 9%. This may not be unexpected as two studies presenting large between group differences, Powell *et al.* (2001) (55.4%) and Fulcher and White (1997) (16.4%); both demonstrating reduction in fatigue in favour of treatment were excluded from this analysis. The prediction interval demonstrated a similar range as the first meta-analysis of a possible greater effect in favour of intervention (-37.5%) to a possible improvement in the comparison group (19.5%). The proportion of future studies estimated to exceed the clinically relevant threshold of 10% was 62%, 64% and 46% in meta-analyses 1, 2 and 3, respectively. Therefore, if the Oxford Criteria case definition is not used, it is estimated that less than half of future studies

conducted in a similar setting would report findings which would exceed the clinically relevant threshold of 10%.

The follow-up meta-analyses used in this review highlight the complexity of this topic and the influence of different diagnostic case definitions, and how these may impact on findings from meta-analyses. This review is the first to consider the impact of removing studies using different diagnostic definitions and as hypothesised by some, this reduced the magnitude of the effect. Based on these findings it is concluded that it is not clear if GET is clinically effective in reducing symptoms of fatigue in people with ME/CFS. Although, the three meta-analyses in this review all demonstrated the direction of the effect was in favour of the intervention.

There was limited data on adverse events in the included papers and these findings support those of Larun *et al.* (2019) that the impact of exercise therapy on serious adverse reactions is unclear. Whilst the included studies did not report a significant number of adverse events there is growing evidence of GET causing harm for some people with ME/CFS. Geraghty *et al.* (2019a) conducted a descriptive survey of people with ME/CFS which reported that 74% of respondents who had undertaken GET reported a worsening of symptoms. This study concluded that GET did not help the majority of people with ME/CFS improve their symptoms and had a negative impact on approximately 50% of respondents. According to Geraghty *et al.* (2019a) GET

also had a negative impact on perceived degree of illness severity in people with ME/CFS.

The difficulty in applying the findings from surveys is that it is not clear how the exercise interventions were delivered and for how long. It should also be recognised that those completing the survey were self-selecting. Furthermore, it is also not clear if those who undertook GET did this individually or with the support of a health care team. Geraghty *et al.* (2019a) theorised that the understanding of those who deliver the intervention could impact on the effectiveness of the intervention itself. They stated that the beliefs of GET therapists had an effect on outcomes, with 80% of respondents stating there was no benefit if the therapist believed ME/CFS to be a psychological illness. Although this was self-reported by the participants themselves and not the health care professionals. Nevertheless, findings from survey data (ME Association, 2015; Geraghty *et al.*, 2019a) appear to contradict the evidence presented in this review and it is not clear why there is such a disparity. It should also be noted that although a large proportion of respondents report a worsening of symptoms, there are a proportion of people with ME/CFS reporting an improvement with incremental exercise (ME Association, 2015; Geraghty *et al.*, 2019a) and it is important to ascertain which sub-group of the population may benefit from a GET intervention.

This review is the first to assess the quality of interventions using a validated framework designed specifically to assess exercise interventions (CERT)

(Slade *et al.*, 2016). Quality of the included studies using this assessment was limited and there was often inadequate description of the exercise component and limited ability to replicate the interventions. The programmes in the included papers were of two general types, the first were interventions where very limited information was provided and statements such as, 'negotiated' or 'incremental exercise was agreed' were provided (Powell *et al.*, 2001; Jason *et al.*, 2007; White *et al.*, 2011; Kos *et al.*, 2015; Clark *et al.*, 2017). The remaining interventions had a specific starting intensity, the time varied between 5-15 minutes, however participants began at 50-60% VO_{2peak} (Broadbent and Coutts, 2016), 50% age predicted maximum heart rate (Moss-Morris *et al.*, 2005), 40% age predicted maximum heart rate (Fulcher and White, 1997) or 70% peak work capacity (Wearden *et al.*, 1998). Demonstrating a range of starting exercise intensities which can prove problematic when attempting to make comparisons across studies.

In a number of the included studies the aim of the intervention was to achieve 30 minutes exercise, 5 days per week at 80% age predicted heart rate (Moss-Morris *et al.*, 2005), 60% VO_{2peak} (Fulcher and White, 1997) or light exercise (White *et al.*, 2011). The data summarised in table 7.9 demonstrates that Moss-Morris *et al.* (2005) aimed for each participant to engage in vigorous activity 5 days per week for 30mins (150mins vigorous) which is greater than the current UK Chief Medical Officers Physical Activity Guidance (DHSC, 2019) for healthy adults (150mins moderate per week or 75 minutes vigorous per week). Fulcher and White (1997) aimed to meet the current guidelines for

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healthy adults (150 minutes moderate activity), while White *et al.*, (2011) aimed for a light exercise intensity (less than recommended for healthy adults).

Table 7.9; Summary of exercise intensities and objective measures.

Intensity category	Measure	Metabolic equivalent
Sedentary	<ul style="list-style-type: none">• < 40% age predicted max HR• < 20% VO_{2peak}	<1.6
Light	<ul style="list-style-type: none">• 40<55% age predicted max HR• 20<40% VO_{2peak}	1.6 < 3
Moderate	<ul style="list-style-type: none">• 55<70% age predicted max HR• 40<60% VO_{2peak}	3 < 6
Vigorous	<ul style="list-style-type: none">• 70<90 age predicted max HR• 60<85% VO_{2peak}	6 < 9

Data taken from Norton et al (2010). HR – heart rate.

None of the included papers inform the reader of how many participants achieved their stated exercise intensity aim at the end of their study. These relatively high exercise intensities maybe due to the underlying belief that there is no physiological component to the illness and therefore participants will be able to achieve exercise intensities similar to healthy adults. Yet studies assessing recovery time during repeat VO_{2peak} tests separated by 24hrs (Hodges *et al.*, 2017), 48 and 72hrs apart (Hodges *et al.*, 2020) demonstrated that the recovery time for repeat high intensity exercise was on average 21 days when separated by 24hrs, 11 days when separated by 48hrs and 5.5

days when separated by 72hrs. Although only based on limited sample sizes (8 ME/CFS vs 8 controls in each group) it would be of interest to have the data relating to how many ME/CFS participants were able to achieve a vigorous level of exercise on 5 days per week.

An area of limited research in ME/CFS is the possible physiological benefits of exercise programmes, when assuming the cognitive behavioural model is incorrect and presuming there is an underlying physiological component of the illness. Broadbent and Coutts (2016) found that peak exercise capacity was increased following 12 weeks of incremental exercise in people with ME/CFS without increasing symptoms of fatigue. It was also stated that although peak exercise capacity was increased in this study from $\sim 20 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $\sim 23/24 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ self-reported symptom severity did not change.

This study also reported that 12 weeks of exercise improved lymphocyte activation without exacerbating symptoms and that 12 weeks of either graded or intermittent exercise increased lymphocyte cell activation to that of the control group. Importantly, in this study participants achieved a physiological improvement, however self-reported symptoms remained the same, or they were able to achieve a greater exercise intensity at the same illness severity. Although this study was conducted on 24 ME/CFS patients across 3 groups and there was no familiarisation to the maximal exercise tests which could mean that any improvement is a learning effect.

Similar findings were noted by Wilshire *et al.* (2018) who conducted a re-analysis of the data from the PACE trial through a freedom of information request. Results from this analysis also demonstrated that GET produces modest enhancements in participants perceived physical function but has little effect on symptom perception. Again, it is feasible that those with ME/CFS were able to achieve higher levels of activity however their symptom severity did not change. Although Wilshire *et al.* (2018) further stated that there were only modest improvements in a 6-minute walk test (67m in GET vs. 30m in control) and no improvement in predicted aerobic fitness using the stop test. Whilst there is lack of clarity of the impact of GET on fatigue, it is also not clear how GET affected overall symptoms of ME/CFS as this was not recorded in the majority of included papers. It is also not clear if physical activity levels were increased in the included studies. It may have been that some were able to increase their physical activity levels while maintaining their symptoms. If this were the case, arguably this could be seen as a positive effect irrespective of any changes in physical fitness, however physical activity levels are not reported directly in the included studies.

The sample in the majority of studies included participants that had a pre-existing psychiatric disorder. Jones *et al.* (2009) discussed the importance of assessing for what they described as 'exclusionary diseases.' That is conditions that someone may have, that would explain their fatigue other than ME/CFS. Jones *et al.* (2009) argued that it is important to ensure those who have a medical or psychiatric condition are not diagnosed with ME/CFS. Jones *et al.* (2009) further stated that to substantiate ME/CFS as a specific condition

or to identify shared pathophysiological factors, subjects fulfilling the criteria of fatiguing illnesses such as ME/CFS, but who have exclusionary and non-exclusionary diagnoses, need to be included as comparison case groups in both mechanistic and therapeutic studies. Strawbridge *et al.* (2019) further stated it is plausible that people with ME/CFS with comorbid depression might have a distinct inflammatory profile from those without, since depression appears to moderate the relationship between hypothalamic-pituitary-adrenal (HPA) axis function and ME/CFS.

Fulcher and White (1997, pg. 2-3) stated in their RCT that participants '*who also had a psychiatric disorder or insomnia were offered treatment... if the treatment was successful but still met the criteria... they were recruited... 27 (41%) had successfully been treated for a comorbid disorder before but still met the criteria for chronic fatigue syndrome*'. The majority of included studies with the exception of Kos *et al.* (2015) reported a proportion of the sample with a comorbid psychiatric disorder yet none of the included studies controlled for this in their analysis. It is therefore unclear what effect this may have had on the overall results for each of the studies. Exercise intervention has been shown to be moderately effective in treating people with depression (Cooney *et al.*, 2013) and this could be a possible factor that could explain the discrepancy between self-reported data from people with ME/CFS and findings from experimental studies.

The ability of an instrument to detect important changes or differences from the patient's perspective or the responsiveness of a measurement tool is an essential aspect of routine clinical practice and as an outcome in clinical trials (Pouchot *et al.*, 2008). However, a consideration of this review is the MCID threshold of 10% which is more conservative than that of the Larun *et al.* (2019) of 7%. Nevertheless, the 7% threshold is deemed to be too low based on the evidence of MCID thresholds for other health conditions. Applying an MCID of 10% at individual study level, 6 of the included papers reported findings below this threshold, however if a threshold of 7% was applied, only 2 papers reported findings below this. The pooled effect of 9% would also have been clinically relevant if the 7% threshold was utilised. Therefore, data which would allow for an anchor-based approach to setting an MCID is essential to compare this data.

The CFQ was the most commonly used instrument in the included papers however a number of studies have reported that the CFQ appears to be the weakest instrument for measuring fatigue in rheumatoid arthritis (Pouchot *et al.*, 2008) and systemic lupus erythematosus (Pettersson *et al.*, 2015). When compared to other fatigue scales such as the FSS and it should be noted that there are no apparent studies which have defined an MCID for fatigue in ME/CFS. Importantly in future studies the MCID for fatigue in ME/CFS should be validated against functional improvements (Goligher *et al.*, 2008).

Findings from this review indicate that the results from the PACE trial (White *et al.*, 2011) did not demonstrate a clinically relevant reduction in fatigue post intervention. Nevertheless, the authors of the PACE trial stated that GET has greater success in reducing symptoms of fatigue than specialist medical care alone. A difference may be due to the data extracted for this review which was taken at 24 weeks (described as post intervention White *et al.*, 2011). However White *et al.* (2011) report their results at 52 weeks post randomisation. The decision to take the 24-week data was to ensure consistency across all studies at taking the study end point and this was the same methodology used in Larun *et al.* (2019). The data taken from 52 weeks post-randomisation are a difference of 3.2 (11-item CFQ – max score 33) or a 9.6% reduction in fatigue.

A final consideration is that advocates of GET in ME/CFS hypothesise that incremental exercise is not just effective in managing ME/CFS but could reverse the cognitions and behaviours that maintain ME/CFS (Clark and White, 2005). If this model were indeed correct and these interventions truly effective, then it could be hypothesised that those with ME/CFS should make a steady recovery and achieve pre-illness levels of activity (Wilshire *et al.*, 2018). However, results from this analysis demonstrate a lack of clarity in regards to possible improvement in symptoms of fatigue. This is supported by Wilshire *et al.* (2018) who stated that there is no data available that would suggest behavioural change interventions based on the cognitive behavioural model achieve the benefits theorised by those who conceived them. Based on the results, future research should consider the applicability of an exercise

intervention to support people with ME/CFS. However, assuming that there is a physiological element of the illness an incremental exercise programme may not reverse the condition but may support those with the illness to be more active.

7.11 Conclusion

In conclusion, it is unclear from the current evidence if GET is effective in reducing symptoms of fatigue in ME/CFS. Studies which provide a much more detailed overview of the exercise intervention need to be conducted so that effective critique of these methods can be made. Stratifying by diagnostic definition in future studies may also allow for more sophisticated analysis which may be able to identify which patients may or may not benefit from incremental exercise interventions. It is also not clear if physical activity levels are affected during the interventions as it may be that there was no significant decrease in symptoms, however participants were able to increase their habitual physical activity. The impact of previous psychiatric disorders should also be considered within the analysis of future studies. Finally, future studies should assess the MCID threshold for symptoms including fatigue for ME/CFS to provide a more accurate indication of the effectiveness of incremental exercise.

Summary of Chapter 7

The findings from this chapter provide a degree of ambiguity regarding the effectiveness of incremental exercise programmes for ME/CFS. Firstly, the use of fatigue as the primary outcome without an objective measure of activity provides a limited overview of the effectiveness of these interventions. It is feasible that participants may have been more active however maintained their symptoms severity (i.e. not exacerbating symptoms) although this is not clear from the included studies. Survey data provides evidence which demonstrated a large proportion of people with ME/CFS who completed the survey reporting a worsening of symptoms following GET. Although the limitations of a self-selected sample may increase the risk of bias, these conclusions appear to contradict the findings from this chapter. The direction of the effect, although not clinically significant, appears to be in favour of treatment. It is not clear if this is due to incremental activity programmes overall, or because of poorly implemented programmes which have not taken into account the unique and complex nature of the condition. There is also limited information about adverse reactions and adverse events and it is difficult to ascertain this information from these studies.

The current theoretical underpinnings of GET in ME/CFS is based on the cognitive behavioural model of ME/CFS. However in chapter 6 it was demonstrated that there may be a physiological element of the illness. It is therefore appropriate to consider exercise or physical activity interventions which assume some physiological component of the illness.

Chapter 8: Perceptions of Exercise and Physical Activity in People with ME/CFS: An Interpretive Phenomenological Analysis

8.0 Introduction

The complexity of the debate associated with exercise and ME/CFS was highlighted in the findings of chapter seven. This chapter provided evidence that when all studies that have assessed GET in ME/CFS were synthesised, exercise was beneficial in reducing symptoms of fatigue. However, this improvement in fatigue reduced after removing studies which relied on the Oxford Criteria case definition. This adds some weight to the arguments made by critics of GET in ME/CFS, that GET may not be effective for all those with ME/CFS (The ME Association, 2015; Geraghty *et al.*, 2019a). These inconsistencies make it difficult to conclude if exercise is beneficial or harmful in the treatment or management of ME/CFS and adds further uncertainty around their relationship.

In chronic health conditions such as ME/CFS where there is ambiguity and uncertainty associated with its medical explanation, those with the illness often become specialists in their condition becoming expert by experience rather than through official medical knowledge (Horton-Salway, 2004 cited in Brown *et al.*, 2017, pg701). This expertise becomes essential when conducting research as those with the illness can provide insights which otherwise may be overlooked (MRC, 2008).

Qualitative research is used to explore perceptions and experiences of a phenomenon from the participant's point of view (Holloway and Wheeler, 2002), to investigate people's understanding of their own lives and social context (Avis *et al.*, 2005). Using this methodology participants are not simply passive subjects but active contributors to the research project. Avis *et al.* (2005) described this as a process of learning from people rather than studying them. Consequently, understanding how people with ME/CFS perceive the role of physical activity and their illness may provide important evidence which could aid the development of strategies that are both effective in terms of symptom management, but also aid in facilitating a return to activity levels which is meaningful to the individual.

There have been a number of qualitative studies which have been conducted in ME/CFS (Larun and Malterud, 2011; Pemberton and Cox, 2014; Broughton *et al.*, 2017). While these studies assess experiences of physical activity in people with ME/CFS, they focus on people already receiving formal treatment (Larun and Malterud, 2011; Broughton *et al.*, 2017), discuss daily living with ME/CFS (Pemberton and Cox, 2014) or recovery from ME/CFS (Brown *et al.*, 2017). Furthermore, studies by Larun and Malterud (2011), Brown *et al.*, (2017) and Broughton *et al.* (2017) did not state an explicit methodological approach which Crotty (1998) argues is essential to understand how the specific method links to the desired outcome and what kind of knowledge can be attained by the research. The study by Pemberton and Cox (2014) used grounded theory methodology and whilst this is a person-centred approach, it

does not allow for the in-depth interpretive analysis that methods such as interpretive phenomenological analysis (IPA) allow (Smith *et al.*, 2012).

There are a number of studies which have used an IPA approach (Edwards *et al.*, 2007; Arroll and Senior, 2008; Dickson *et al.*, 2008; Arroll and Howard, 2013; Wilde *et al.*, 2019), although, these studies have focused on identity (Dickson *et al.*, 2008; Arroll and Howard, 2013), stigmatisation in men with ME/CFS (Wilde *et al.*, 2019) or have taken a broader view of the condition (Edwards *et al.*, 2007; Arroll and Senior, 2008). However, it appears no studies have used an IPA approach to explore the perceptions of physical activity in people with ME/CFS.

This study will consider both exercise and physical activity. The reason for this is that those who have ME/CFS may not be engaged in exercise however may be undertaking some degree of physical activity. The aim is to understand how people with ME/CFS perceive physical activity and exercise and their illness. Katzmarzyk *et al.* (2017) states that,

'physical activity refers to any bodily movement produced by the skeletal muscles that results in energy expenditure above resting levels whereas exercise is physical activity that is usually performed repeatedly over an extended period of time for the purpose of increasing aerobic or muscular physical fitness, improving health, and/or improving sport performance' (Katzmarzyk *et al.*, 2017).

Exploring the Relationship between Physical Activity and ME/CFS

Physical activity can occur in many contexts and it is most often considered within the domains of leisure-time, occupational, transport, and household chores (Katzmarzyk *et al.*, 2017). The purpose of this study is to explore the impact of all activity including tasks of daily living such as personal care, housework, gardening as well as structured exercise on ME/CFS. Therefore the aim of this study is to explore the experiences of physical activity and exercise in people with ME/CFS.

8.1 Aim

The aim of this study was to explore the experiences of physical activity and exercise in people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

8.1.1 Change in phrasing; CFS/ME to ME/CFS

It should be noted that all documentation in relation to this study (appendices F to P) used the phrasing chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and this choice of phrasing was guided by the NICE (2007) guidelines. However, during the process of writing this thesis this phrasing was changed to align with the now internationally recognised phrasing; ME/CFS. This does not impact on any theories or discussion points raised however this change was made to ensure consistency with current contemporary ME/CFS literature.

8.2 Planning and Ethical Approval

This study was not registered with any online database. However, several registration platforms were considered including Research Registry (<https://www.researchregistry.com/>). The decision was made not to register with this database as there was a fee and the research team believed this was counter to the ethos of protocol registration. At the time of conducting the study the research team were unaware of other appropriate registration databases for qualitative research. The consolidated criteria for reporting qualitative research (COREQ) (Tong *et al.*, 2007) was used in the reporting of this study.

During the development of the study the decision was made to invite a fourth member to join the research team (SH (Reader – Research, Teesside University)), as SH had more experience and specialised knowledge in qualitative methods and analysis. The study was reviewed by SH and modifications were discussed to enhance the design and ensure the procedures were congruent with the overall methodological approach. For example, initially this study was going to include a form of member checking however following discussions this was removed as member checking is not compatible with the chosen methodology.

The study was approved by the following ethics committees and public bodies before data collection began: 1) Teesside University School of Health and Social Care Research Ethics Committee (appendix F, pg. 327) 2) West of Scotland Research Ethics Committee 3 (appendix G, pg. 330) 3) Health Research Authority (HRA) Approval (appendix H, pg. 334) 4) local approval

from research and development (R&D) department of the NHS trust where recruitment took place (appendix I, pg. 342).

8.3 Method and theoretical underpinnings

The chosen method for this study is interpretive phenomenological analysis (IPA) which is underpinned by the theoretical perspectives of interpretive phenomenology, hermeneutics and idiography (Smith *et al.*, 2009; Pietkiewicz and Smith, 2014; Peat *et al.*, 2019). Phenomenology was originally devised by Husserl in the 1930's as a way to understand the lived experiences of people (Alase, 2017). It aims to identify the essential components of phenomena or experience that make them unique or distinguishable (Pietkiewicz and Smith, 2014). Phenomenological studies focus on how people perceive and speak about objects and events, rather than describing phenomena according to a predetermined criterion (Pietkiewicz and Smith, 2014). Smith *et al.* (2009) stated that phenomenologists have a particular interest in thinking about what the experience of being human is like, in all its various aspects, but especially in terms of the things which matter to us and constitute our lived world. From a phenomenological perspective, we are interested in an experience that has particular significance and importance to the participants and the "parts of life" that influence that experience (Smith *et al.*, 2009).

This led to what Heidegger described as the concept of Dasein or the study of 'there-being' (Crotty, 1998). In effect the question of existence itself. Heidegger implies that our very nature is to be there always somewhere, always located and always amidst and involved with some kind of meaningful context (Larkin

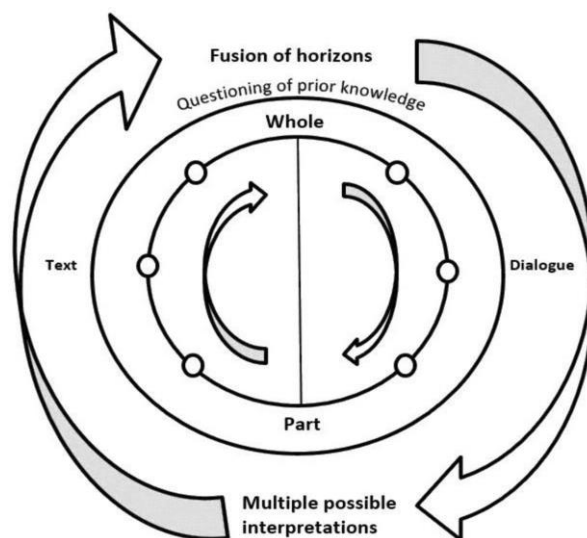
et al., 2006). Heidegger also introduced the concept of intersubjectivity, which aims to explain our relationship with the world, Heidegger argued that a fundamental part of being is our relationship to the world (Smith *et al.*, 2009). *'Intersubjectivity is the concept that aims to describe this relatedness and to account for our ability to communicate with, and make sense of, each other'* (Smith *et al.*, 2009).

IPA is also underpinned by hermeneutics, which is the theory of interpretation (Smith *et al.*, 2009; Peat *et al.*, 2019). Whilst phenomenology uncovers meaning, hermeneutics aims to interpret meaning (Pringle *et al.*, 2011). Peat *et al.* (2019) argued that while IPA researchers view the participant as the experiential expert, they acknowledge that experience cannot be simply revealed. Peat *et al.* (2019) stated that a process of rich engagement and interpretation involving both the researcher and researched is required, involving an ongoing reflective process by the researcher. Smith *et al.* (2009) stated that IPA researchers engage in a double hermeneutic process. Firstly, the participants are trying to create meaning of their personal and social world. Secondly, the researcher tries to decode that meaning to make sense of the participants experience. However, unlike the participant, the researcher only has access to the participants perceptions through the information that is provided during data collection (Smith *et al.*, 2009). It is important to acknowledge however, that Smith *et al.* (2009) further argues that interpretation is contextualised in previous experience (Shinebourne, 2011). That is, that interpretation is based on *'something we have in advance'* (Shinebourne, 2011). As the researchers can only access the participant's

experience through the information provided by the participants, alongside the researcher's own experiences.

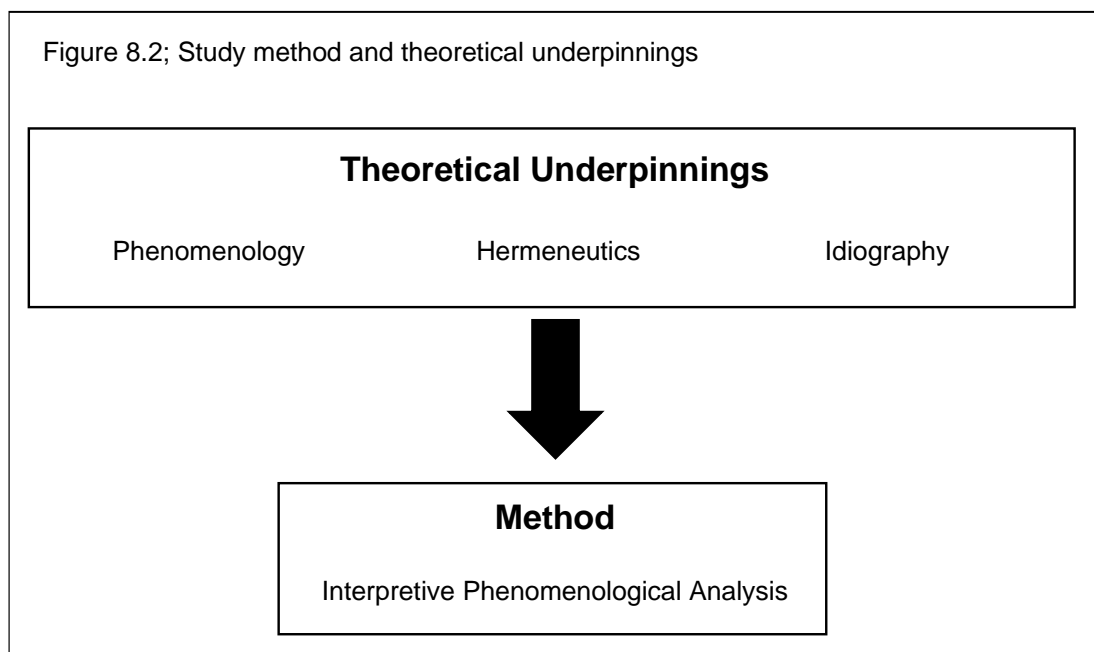
The hermeneutic cycle, which describes the way in which IPA researchers interpret data utilises the concept of 'the part' and 'the whole' (Smith *et al.*, 2009). Smith *et al.* (2009) described this process, in that we only understand the meaning of individual words when they are placed within the context of a sentence. However, the sentence itself only has meaning because of the combination of words. Smith *et al.* (2009) argued that it is this moving between these two, the part and the whole, that we are able to interpret the experience of the participants. Adding that, as data is analysed the researcher does not move through linear stages, instead moves between the part and the whole depending on the stage of the cycle (Smith *et al.*, 2009). Figure 8.1 provides a visual representation of this process.

Figure 8.1; Diagram of the hermeneutic cycle associated with IPA. Taken from Peat et al. (2019).



Another theoretical underpinning of IPA is idiography, defined by Pietkiewicz and Smith (2014, pg. 8) as '*an in-depth analysis of single cases and examining individual perspectives of study participants in their unique contexts*'. Using this approach each case (or participant) is considered individually before producing any general statements (Smith *et al.*, 2009). This differs from quantitative or positivist perspectives in which groups and/ or populations are studied to assess for change and effect relationships, or associations between variables to make inferences based on these observations (Holloway and Wheeler, 2002). Like all qualitative research, IPA is a method focused on the individual account using distinct narratives to illustrate the experience of those in the study, whilst also demonstrating similarities and differences between those individual accounts (Pietkiewicz and Smith, 2014).

Figure 8.2; Study method and theoretical underpinnings



The chosen method underpinned by these theoretical underpinnings is IPA. From an IPA perspective, human beings are self-interpreting beings; that they are continually interpreting the objects, events and people in their lives (Smith *et al.*, 2009; Pietkiewicz and Smith, 2014). IPA researchers aim to understand what it is like to experience a phenomena or event from the participants points of view. Pietkiewicz and Smith, (2014) described this as, '*like standing in the shoes of their subjects*' not only to understand how individuals make sense of their world and how they experience events, but also what meaning they attribute to their experiences. Shinebourne (2011) stated that IPA is concerned with how meanings are constructed by individuals within both their social and their personal world. Therefore, in IPA the researcher (or interpreter) takes a central and '*active*' role in making sense of the personal experience (Pringle *et al.*, 2011). The researcher is not simply describing emerging themes and instead attempts to fully uncover the experience under study (Pringle *et al.*, 2011). In essence, in IPA the researcher is not necessarily interested in the topic per se, instead they are interested in a particular person's perceptions of the topic and their understanding of it (Larkin *et al.*, 2006). Larkin *et al.* (2006) further argued that in IPA the researcher must take on two approaches, the first to describe '*what it is like*'. The second involves the researcher developing a more interpretive analysis which positions the initial 'description' in relation to a wider social, cultural, and perhaps even theoretical context (Larkin *et al.*, 2006). Importantly, IPA considers the person as embodied and embedded in the world, in a particular historical, social and cultural context (Shinebourne, 2011). Therefore, this was deemed to be an appropriate method to investigate the topic of physical activity and exercise in ME/CFS.

8.3.1 Reflexivity

Smith *et al.*, (2009) argued that two concepts are essential in IPA research. Bracketing, described by Morrow (2005) as 'monitoring of self' or being 'rigorously subjective' is the process by which the researcher makes effort to articulate their own perspectives. By making an attempt to become aware of their own implicit assumptions and predispositions on the subject, to ensure the perspectives discussed are truly those of the participants in the study (Morrow, 2005). Morrow (2005) stated that once identified these should be set aside to prevent them unduly influencing the study. Although Morrow (2005) acknowledges that it has been argued that it is impossible to fully know all our preconceptions on a topic.

Peat *et al.*, (2019) stated when using an IPA approach the researcher needs to be mindful of their own beliefs, perceptions and experiences so that they can enrich their interpretations rather than these becoming a barrier to making sense of the participant's experiences. This is achieved through the process of reflexivity (Peat *et al.*, 2019). Tong *et al.*, (2007) stated that researchers should recognise and clarify for readers their identity, occupation, sex, experience and training. This improves the credibility of the findings by giving readers the ability to assess how these factors might have influenced the researchers' observations and interpretations (Tong *et al.*, 2007).

JF is a male Senior Lecturer in Research Methods at Teesside University. He is undertaking his PhD in physical activity and ME/CFS, part time at Teesside University and this study is a component of this thesis. His background is Sport

and Exercise, with undergraduate and postgraduate degrees in this field. The primary researchers background is quantitative research methods, and this is his first qualitative research study. No formal training was undertaken prior to the commencement of the study. Although, JF had undertaken professional development courses at Teesside University which had involved the development of skills such as active listening and allowing space in discussions for people to explore their thoughts and beliefs on a topic. SH also provided mentorship and guidance throughout the design, data collection, analysis and interpretation stages of the study. Throughout the study, ideas were reflected upon and discussions took place with the research team to try and maintain neutrality and confirmability during the study.

Discussions also took place between JF and SH about qualitative data collection, specifically about the creation of questions and how to allow for flexibility in the data collection process. The primary researcher's interest in exploring ME/CFS research followed a family member's diagnosis of the condition when he was a child and subsequent exposure to the condition through childhood and into adulthood.

SH is a physiotherapist and reader in Respiratory Rehabilitation at Teesside University. She completed a PhD in psychology and her expertise is in chronic breathlessness. SH has extensive experience in qualitative research including IPA.

AB is a professor at Teesside University involved in interdisciplinary research with broad interests and expertise in physical activity, exercise and health outcomes, measurement and evaluation issues, and research design and biostatistics. He is a Fellow of the American College of Sports Medicine (ACSM) and the Royal Statistical Society and a Statistics Consultant for the three journals of the Physiological Society.

GA is a Professor of Health Sciences and Biostatistics Research at Teesside University. His interests focus on the translation of knowledge about human physiology to real world problems. He is a Fellow of the Royal Statistical Society and has published widely in research methods and statistics. GA also has interest in general exercise science, particularly the relationships between physical activity and cardiovascular health.

8.4 Methods

8.4.1 Participants

The eligibility criteria for entry into the study were adults (18yrs+) with current diagnosis of ME/CFS and an existing outpatient at an CFS/ME Clinic at a large trauma centre in the north east of England during December 2017 and June 2018. The diagnostic definition used at this clinic was NICE (2007). No further ME/CFS screening took place by the research team. Participants were excluded if they required a translator to participate or were deemed by the direct healthcare team to not have capacity to give informed consent.

The direct health care team acted as gatekeepers on behalf of the research team. They were asked to identify individuals who met the inclusion criteria and they believed would provide a rich and detailed description of their experiences. In line with Smith *et al.* (2009) the aim was to recruit a homogenous sample of participants through convenience sampling of individuals with the same diagnosis and from the same clinic. This has been described as an appropriate sampling strategy for IPA (Pietkiewicz and Smith, 2014; Alase, 2017). The use of gatekeepers was to ensure that only those who had legitimate access to the patient group made the initial contact. Potential participants were then provided with the initial contact form (appendix J, pg. 343), the participant information sheet (appendix K, pg. 345) and a consent form (appendix L, pg. 350). If a patient volunteered for participation in the study, they were then required to either phone or email the primary researcher to declare their interest in the study.

The intended sample size for this study was eight, in line with Smith *et al.* (2009) recommendations however, the final sample size was six. IPA studies involve highly intensive and detailed analysis of the accounts produced by a comparatively small number of participants and between six and eight participants is an ideal sample size for an IPA study (Larkin *et al.*, 2006). Smith *et al.* (2009) further argued that IPA studies are conducted on relatively small samples and designed to gain a thick and rich description of the lived experience. Although six participants was less than originally intended, Smith *et al.* (2009) stated that six participants would provide the depth of data

required to provide an effective analysis of the experience and that IPA studies should focus on the '*quality and not the quantity*' of data.

On reflection, following the data collection period, it may have been more effective for JF to be available to potential participants to explain the study in person immediately following the initial contact by the gatekeeper. Graffy *et al.* (2008) demonstrated that key aspects of recruitment in health care include, building and maintaining relationship and providing clear information to participants. By using a face to face discussion during recruitment this could have aided with building a rapport with potential participants as well as providing an opportunity to ask any questions. Information relating to the number of people who were provided with the study information by the direct healthcare team but did not contact the research team was not recorded. All participants who contacted the research team were included in the study, with no participant dropping out of the study. One participant contacted the research team after the data collection period had finished, this person was not interviewed. There was no prior relationship between the research team and any participants, however they were informed that this study would form a component of JF's PhD thesis.

8.4.2 Data Collection

If a potential participant wanted to proceed, a date and location was agreed at least 7 days from the date the participant contacted JF. Participants were invited to take part in an in-depth interview either in a private room at Teesside University or at the participant's home. This location was decided by the

participant. When conducting a qualitative study, the location of the interviews becomes important because setting can influence responses (Smith *et al.*, 2009). Elwood and Martin (2000) discussed the importance of ‘placing’ interviews. Stating that,

‘the interview site itself embodies and constitutes multiple scales of spatial relations and meaning, which construct the power and positionality of participants in relation to the people, places, and interactions discussed in the interview.’

The importance of “placing” the research, and where the participant places the researcher will impact on how they respond (Elwood and Martin, 2000). For example, in the university setting they may place JF as a lecturer, and possibly perceive this as more powerful than themselves in this setting. In a hospital clinic they may be reluctant to talk openly due to previous experiences with health care professionals. Elwood and Martin (2000) argued that interviews conducted in participants’ homes have important potential as a strategy for disrupting power hierarchies between researchers and participants. Five interviews took place at the participant’s home; one interview took place at Teesside University. All interviews took place with the interviewer and interviewee only. All interviews were conducted by JF.

The method of data collection used in this study was in-depth interviews. Pietkiewicz and Smith (2014) stated that the primary aim of an IPA study is to elicit rich, detailed and first-person accounts of experiences and phenomena

under investigation and that in-depth interviews are an effective data collection method to achieve this. Further adding that this allowed for participants to engage in discussion in real time and give enough space and flexibility to allow for the exploration of topics that arise during the interview process. However Pringle *et al.* (2011) stated that although an IPA approach has enough flexibility to allow for a variety of different data collection methods. The limitations are not always discussed in sufficient detail and advises researchers to acknowledge and discuss the advantages and disadvantages of their chosen data collection methods. For example, face to face interviews may not allow the time and space for the participant to consider their answers. Other non-face to face methods could have been used to help create a non-threatening and comfortable environment, which may have provided greater ease for participants discussing sensitive issues (Alase, 2017). Although, at the start of each interview, 5 minutes was spent asking participants about how they were, to try and establish rapport.

Before the interviews took place, participants were given information about the study and provided with an opportunity to ask any questions. Participants were then asked to sign an informed consent form before the interviews took place. In accordance with the Declaration of Helsinki (World Medical Association, 2013), as involvement in research must be voluntary. Demographic information was collected including age, sex, and number of years they have been diagnosed with ME/CFS and the number of years they believe they have been ill (this may differ from the official diagnosis). Interviews lasted between 45 and 60 minutes and were recorded using a Dictaphone which was then

transcribed verbatim by JF. The use of in-depth interviews allowed the researcher to make use of prompts and probing, which provided the participants the opportunity to explore topics that the researcher believed to be important to the research question and aims (Smith *et al.*, 2009). Limited field notes were taken during the interviews and used when transcribing the interviews.

The questions were informed by previous qualitative work in this field including the study by Larun and Maltrund (2011). These were then discussed with the research team and refined, before scrutiny by the relevant research ethics committees. The interview schedule can be found in appendix M, pg. 353.

During the interviews, the wording of questions varied slightly to maintain the flow of the discussion although the key aspects of each of the questions remained the same. Prompts were used during the interviews, however this was used at JF's discretion when it was thought it would be beneficial for a participant to explore a topic in more detail. Pringle *et al.*, (2011) reported that expansive, honest and reflective accounts may be less forthcoming and more difficult to access from participants if a rigid set of questions or a more structured interviewing technique are used. Following each interview, a process of reflexivity was undertaken to consider why particular topics were explored in more depth and not others. The use of a reflective diary was important as it was noted that Smith *et al.* (2009) stated that the researcher may not be aware of pre-conceptions in advance and therefore it was important to undertake an on-going process of reflection.

If a participant began to get distressed they were asked if they wanted to pause the interview and resume when ready. If needed, they would be asked if they wanted to terminate the interview. In two of the interviews the participant was asked if they wanted to take a break; a comfort break was taken in one interview. On the second occasion, a participant began to demonstrate signs of becoming upset however they decided to continue the interview. Participants were informed that they could withdraw from the study up until 31st December 2017 initially, however due to slow recruitment the data collection period was extended, and the withdrawal date extended to the 1st June 2018. As no contact information was kept, those who participated in the study before the 31st January were not informed of the extension to the data collection period. No participants withdrew from the study. A letter was written to each of the participants' general practitioners (GPs) to notify them of their participation in the study. No action was required on the part of the GP. A template of this letter can be found in appendix N, pg. 354.

8.4.3 Data Analysis

Avis (2005) stated that an important aspect of qualitative data is analysing textual data as this allows people to express their thoughts and beliefs in their own words and on their own terms. Further adding that there is a responsibility to analyse and present textual data in a way that preserves their narrative (Avis, 2005). The process of analysis involved the following 5 stages and is underpinned by IPA (Smith *et al.*, 2009).

Stage 1; Transcribing, familiarisation and initial coding

JF transcribed the interviews verbatim and familiarised himself with the transcripts by undertaking several active reads of the texts. Following this a line-by-line analysis of the transcripts was conducted. This involved the initial identification of emergent patterns and themes and the beginning of a more in-depth analysis where consideration was given to the interpretation of the generated codes. The codes were derived from the data and a reflexive diary was kept throughout this process. This stage also involved the development of a clear overview of how the analysed data can be traced through the research process using QSR International's NVivo 12 qualitative data analysis software. During this first stage, connections between emerging themes were considered and grouped together where appropriate (Smith *et al.*, 2009). This produced a large list of emerging codes that were discussed in the second stage of analysis.

Each transcript was analysed individually to ensure an idiographic approach was maintained as described by Smith *et al.* (2009). Nevertheless, it should be acknowledged that it proved challenging to 'bracket' any initial thoughts/ideas that arose from the earlier transcripts when analysing subsequent transcripts. Although JF attempted to analyse each individual transcript on its own terms, it became apparent through the process of analysis that data generated in the analysis of the earlier transcript could not be completely bracketed from informing the interpretation of the later transcripts. Nevertheless, JF reflected on this process and after consideration felt this did not prevent the emergence of new themes.

Stage 2; Peer review

The aim of the peer review process and discussion was to facilitate a deeper understanding of the topic, however JF remained the principle interpreter of the data. When using an IPA approach to analyse the data it is important to acknowledge that individuals (or the participants) make sense of the world through the everyday human resources available to them (Smith *et al.*, 2009). Access to this experience is only available through the information that is provided by the participant and this information is then interpreted through the 'experiential lens' of the primary researcher (Smith *et al.*, 2009). Through this peer review process the aim was to 'broaden' this lens to provide greater depth of interpretation.

Prior to the stage 2 process, JF and SH had an initial meeting and JF provided an overview of his initial codes and reflections on the transcripts and analysis. In this process, development of emerging themes were discussed. SH then read and analysed two transcripts and familiarised herself with the data prior to a full peer review discussion which took place approximately two weeks later. During the peer review process SH discussed her interpretations from the two transcripts and discussed her interpretations of the data. The discussion then moved back to JF's original analysis and a discussion took place around similarities, differences and any deeper interpretations that had developed as a result of this process. Importantly, during this process in accordance with the IPA approach described by Smith *et al.* (2009) discussion took place in relation to convergence and divergence as opposed to solely focusing on commonalities as with a more traditional phenomenological

approach (Pringle *et al.*, 2011). Following this meeting, JF reflected on this discussion and applied these findings to the whole data set. This resulted in the development of master themes.

Stage 3; Involvement of patients in the interpretation

As part of this thesis a Patient Public Involvement (PPI) group was created (Teesside University CFS/ME Patient Advisory Group (PAG)) to provide patient input into studies in ME/CFS that may arise from this work. To support the development of a more in-depth understanding of the topic, the developing themes were shared with the PPI group. The PPI group included 9 people with ME/CFS who were all recruited through a post on the ME North East Facebook page (Advert in appendix O, pg. 356). Those interested were asked to contact JF directly. Once included, members of the PAG were informed they could discuss face to face, over the phone or discuss via email depending on which method they preferred. No formal ME/CFS screening took place and for the purposes of this group anyone who declared themselves as having ME/CFS could be included. No demographic information in relation to individuals in this group was collected.

As with the peer review process, JF remained the principle interpreter of the data however the aim of this process was to allow JF the opportunity to reflect on the interpretations to provide a more in-depth analysis of the experiences. Those involved with the PAG were sent a copy of the major themes and supporting quotes and asked to comment. The information sent to the PAG can be found in appendix P pg. 358. No member of this group was sent any

participant identifiable information and no identifiable information was collected from the PAG members however their comments were used to illicit a deeper understanding of the patterns and recurring themes implicit within the experiences.

Feedback was provided by 6 members of the PAG. All members commented that they thought the themes accurately reflected their experiences. Two members fed back that they found the process of reading over the comments quite emotional as they could relate to the experiences on a personal level. Other comments were made in relation to the existing themes which added more depth and provided personal experiences from PAG members. Sub themes were reinforced, such as hypersensitivity impacting on the feelings of isolation. Lack of information by healthcare professionals which reinforced a feeling of misunderstanding of the condition. Feeling the illness is hidden and feelings of lack of legitimacy about their illness. One member also asked the researcher to consider the language used such as 'fear' as they felt these were quite medical terms and asked the research team to consider language such as apprehension. Following the PPI process, JF considered their comments in relation to the master themes and this information was discussed with the research team.

Stage 4; Discussion of interpretations with whole research team

In this stage of data analysis, a discussion took place with the research team to discuss the interpretations. This discussion included AB (Professor in Exercise Science, Teesside University), GA (Professor in Health Science and

Biostatistics, Teesside University) as well as JF and SH. During this process JF talked through the master themes and how the sub-themes related to each master theme. JF then provided feedback from the PPI group and informed the research team how this feedback had contributed to the interpretations. An open discussion then took place and the research team were invited to challenge these interpretations and provide insight through their own experiences. Following this discussion, JF reflected on the input from the research team and considered the master themes and narrative to ensure the coherence and plausibility of the interpretations.

Stage 4; Developing a deeper level of interpretation

Smith *et al.* (2009) stated that a common criticism of IPA research is that it is often too descriptive. Especially when conducted by novice researchers who may be too cautious in their analysis. Therefore, time was taken to consider the master themes and codes developed during the analysis and consider if there was any other deeper level of interpretation that could be developed. This process was conducted over several months and involved JF reading over and considering the themes. During this process no new themes were developed however JF attempted to consider the interpretation while developing the narrative.

Stage 5; Developing a full narrative

In the final phase of analysis JF refined the themes and a full narrative was developed with quotes from participants, as supported by Pringle *et al.* (2011) who stated that '*the aim of IPA is to illustrate, inform and master themes by*

firmly anchoring findings in direct quotes from participant accounts'. The narrative was refined before this was shared with AB, GA and SH to review.

8.5 Findings

Six people with a confirmed diagnosis of ME/CFS participated in in-depth interviews lasting between 49 and 83 minutes. The individual demographic information can be found in table 8.1. The sample included three men and three women with an average age of 47.6 ± 8.1 yrs. The number of years that they believe they have been ill (including before diagnosis) ranged from 1.5 – 4 yrs. Those included within the study had an approximate diagnosis of ME/CFS of between 1 – 2.5 yrs. Demographic information is missing for one participant (participant 5).

Table 8.1; Demographic information of participants

Participant	Age (years)	Sex	Approximate number of years ill	Approximate number of years diagnosed	Length of interview (mins)
1	54	Male	4	2	62
2	47	Female	5	2	49
3	43	Male	3	2.5	70
4	37	Female	1.5	1	44
5	-	Male	-	-	83
6	57	Female	3	2	59

Four superordinate themes were identified through the analytical process and are summarised in table 8.2. However, we believe these four themes are interwoven and are not separate entities, due to this there is some cross-over. The first theme identified was 'I won't let it beat me'. This theme related to how participants spoke of trying to 'hit it head on' and believing they could beat the illness if they just persevered. This was accompanied with war analogies and describing the process as battling, and I won't give in. However, participants describe how this approach resulted in a significant worsening of symptoms and often periods of significant illness.

The second theme was 'Losing sense of self'. This theme related to how participants discussed how the illness had brought a fundamental change to their day to day living. In particular participants describe no longer being able to participate in normal tasks of living such as employment, parenting or socialising. With this resulting in strong feelings of isolation and low mood and a loss in confidence. This theme also continued the relationship of mood and activity and how completing/ engaging in activity tasks can provide some improvement in mood.

The third theme generated in this study is 'Hiding symptoms but seeking compassion'. This theme relates to the hidden nature of this illness and how this can create a feeling of lack of legitimacy in people with ME/CFS about their illness. We also noted participants describing a fear of negative evaluation of others, often trying to hide how ill they felt. Finally, this theme

related to how participants described wanting empathy and understanding of their condition.

The fourth theme generated in this study we have labelled 'Small wins and flexible approach'. This theme related to how participants describe wanting to do more, which is related to theme two, the loss of self. However, more specifically this theme related to how participants describe needing to plan for activity however the illness can still catch them out. This theme also relates to the unpredictability of the condition and how flexibility is essential.

Table 8.2; superordinate themes and sub-themes

Superordinate theme	I won't let it beat me	Losing sense of self	Hiding symptoms but seeking compassion	Small wins and flexible approach
Sub-themes	Reaching crisis point	Fundamental change	Hidden illness	Wanting to do more
	Getting worse even though I've slowed down	Loss of role/ family role	Feelings of lack of legitimacy	Consequences of doing too much
	Crippling exhaustion	Lack of socialising/ engaging in societal activities	Fear of negative evaluation	Unpredictability
		Isolation	Wanting people to understand	Requires a flexible approach
	Trying to hit it head on	Forgetfulness	Wanting empathy	It still catches me out
		Loss of confidence		
		Activity and mood		

1. I won't let it beat me

Participants describe trying to beat their illness and trying to hit it head on, which results in a worsening of symptoms. Individuals emphasise feeling exhausted forcing them to slow down, yet the illness continued to worsen leading to feelings of frustration and hopelessness. In particular participants perceive the illness to be a weakness harbouring the belief that it can be 'beaten'.

1.1 Reaching crisis point

Feelings of frustration with trying to get a diagnosis were prominent throughout the narrative and this was coupled with relief when a diagnosis was received. However, in the process leading up to getting a diagnosis, participants reach a crisis point in the management of their symptoms becoming overwhelmed before seeking help, *'I was trying to get back to normal and, the tiredness and the pain just got worse. In fact, it got to a point where I couldn't really move off the settee, I was in that much pain. I then started going to the GP...'* P1. Participants often delay seeking care as they ascribe symptoms to 'just getting old' or just 'one of those things'.

1.2 Continued to get worse even after slowing down

Participants described a period when they became ill when they had made initial modifications to their lifestyle however their symptoms continued to deteriorate, *'once I finished work... you think you'd get better, you know by not putting that extra pressure on, but it seemed to get worse, as in more, more fatigue...'* P5. This linked to possible denial of having a chronic illness and that

they will recover, *'the doctor saying to me look you're just going to have taken at least a month out... took me back to see my doctor and I said to her, I'm really sorry, but I said to her, I feel worse after the month off and she said, I expected that you would, and, she was just talking to me and she just, like said to me, you need to take another three months off'* P6.

1.3 Crippling exhaustion

Individuals describe being in constant pain and experiencing tiredness, mental exhaustion and emotional fatigue. Participants discuss initially trying to 'beat' the illness or 'hit head on'. *'I thought, oh, I can fight my way through this, if I battle on, if I push myself really hard, what will happen is I'll sort of, crack it and I'll be fine'* P1. Notably language and metaphors around 'battling' and conflict frequently appeared in patients' narratives, emphasising their state of alertness due to the fluctuating disease requiring constant monitoring.

A period of battling or try to hit it head on, was followed, in the majority of cases, by a significant worsening of symptoms, *'I was like, I won't be beaten, I'm just going to push myself, I'm going to do it, and I made myself so ill, I ended up in bed for days, I couldn't physically move and it terrified me'* P2. However, this contrasted with language used by participant 6 which portrayed self-blame *'I remember beating myself up and thinking, that, almost blaming myself for my body giving up'*. This led to feelings of despair and hopelessness.

Participants emphasise how the process of being ill was overwhelming, *'initially it was overwhelming, the fatigue, to the point that, at its worst, I couldn't, the energy required to get out of bed'* P6. This was echoed by participant 3 whose narratives describe an episode of extreme exhaustion. *'I remember it being very, very hard, was, when you're feeling so tired, all you want to do is lie down and you don't want to engage and you just want to sleep... it was so much more than any level of normal tiredness... it was a totally different extreme'* P3. This resulted in a period of inactivity leading to feelings of helplessness, depression and sadness.

2. Losing sense of self

2.1 Fundamental change

Participants spoke of how the illness had fundamentally changed them, *'I kept thinking, I was becoming a person that I didn't recognise and I think it fundamentally, looking back, it must have just been because I was so tired, I just didn't trust my thoughts or didn't trust my, I don't know, just didn't trust in myself anymore,'* P6 which was frightening and created a sense of confusion.

Participant 3 used language of detachment, giving a sense as though he is seeing someone else, he did not recognise, *'probably sounds a little bizarre but you were almost removed from your own being... I was almost following myself as in I was, my consciousness was almost removed from my physical self... a feeling of being totally detached... I felt like I was just going through the motions... it was a general feeling of detachment'*. The participant describes not only losing a sense of self but also a loss of everything and

consequently, they no longer knew who they were. This produced feelings of confusion and fear.

2.2 Loss of role

The three male participants used language to define the fatigue associated with ME/CFS as being different to a fatigue that has '*been earned*'. We interpret this as possible feelings that they were losing their role as a provider. Referring to a point in time when they had, from their point of view, earned the right to be fatigued. This contrasts to how they feel now that their fatigue has not been earned, which further exacerbating the feelings of losing who they were and feelings of despair. When describing an occasion before participant 3 was ill with ME/CFS he gave the example, '*You've almost got to the point where you've earned the right to feel a bit tired because you've had a really productive day, you've had a really busy day and you've achieved a lot and you know, you get to that point where you think, blimey that was a good day, I now need to get a good night sleep.*' P3. The implication being that how they feel now has not been 'earned'.

Participants emphasised this further when discussing the loss of the family role, again depicting a sense of losing the role within the family unit. '*I say active because obviously... we used to, be very active, go on a lot of walks and things like that, [local landmark], is a good example. We'd go up there take the dog. Lots of woodland walks, that kind of thing*' P1.

P1 also described how the illness changed his appearance *'but I couldn't stand anything that was touching me, in fact the reason I ended up growing a beard is because I couldn't have a razor near my face, it's sort of everything set me off, it was that sensitive to it'*. This combination of feeling as if they had lost their traditional role in the family, specifically no longer being able to provide and changes in appearance all contributing to this feeling of losing identity. *'They say that I look, I look tired and they say that I, they say I change colour, that I drain colour and things like that, and they say that I fade away. They say it's like a light's on but nobody's at home' P6.*

2.3 Isolating

Along with this, the six participants discussed the impact of the illness on their ability to socialise. *'I would like to get to a point where I do have more energy to do fun stuff but I guess that's just part of it, isn't it, that the fun stuff goes, that's the first thing to go, is anything fun,' P4.* Participant 3 described the frustration at not being able to participate in normal social activities *'it was also affecting friendships, where normally people would actually contact me and say, you know, do you fancy doing something at the weekend or do you fancy doing this evening after work, and I had absolutely no energy to do it'*. Isolation was a strong theme throughout the participant narratives. Participants would often make reference to not being able to socialise, this fundamental change from who they were, alongside these feelings of isolation resulting in feelings of sadness and resentment at not be able to participate in everyday life.

2.6 Mood and activity

Participants provided strong insight into these feelings, however there was also discussion around how completing a task/ achievement was associated with an increase in mood, *'yes, I'm really pleased that happened and you sort of get that feeling of elation and as a result, my energy levels would go up, but just for a short period of time, and then they would dip again'* P3. We believe this may be linked to participating in activities prior to illness being linked to a feeling of re-finding a 'sense of self'. That is, engagement in societal activities provides some sense of 'being me' which led to a subsequent improvement in mood and symptoms.

3. Hiding symptoms but seeking compassion

This theme relates to how participants feel ill, while also being aware that from the point of view of others, they appear well. This links to the hidden nature of the illness which results in a feeling of lack of legitimacy around their illness and a fear of negative evaluation by others and a subsequent desire for empathy and understanding.

3.1 Hidden illness

The participants spoke of how they felt that some people did not believe they were ill, which at times may have resulted participants questioning their illness themselves. However, the uncertainty around diagnosis, treatment left participants in a 'no-man's land' with no external indication of 'illness', and therefore no indication of 'wellness' *'I guess what I'm trying to share is that if I'd had some illness that was, you know, easily recognisable, easily*

diagnosable, treatable, I wouldn't have had an issue with that... because it's this ambiguous illness... got this huge question mark about it from some people' P6

Participants were aware that they had to be having a really bad day for the illness to be 'visible' and there was an awareness that they didn't *look* like someone who was ill. *'She doesn't realise how bad I am until something like I can't get up from the table or something like that... you see at work they just see me getting on with it and they don't sort of see, it's the bit at home' P4.* On one hand the illness is invisible yet it has a visible impact on appearance when its most severe. However, the hidden nature reinforcing the loneliness of being chronically ill, *'they don't realise how, when I take my make-up off and stuff, that I feel really ill' P2.*

3.2 Feeling a lack of legitimacy

Emotionally charged language was used to describe the illness which again was attribute to wanting to emphasise the seriousness of the condition and linked to feelings that they need to convince people that they are indeed ill. *'Crippling's of chest pains'* and *'almost like something was gnawing away at it'* P1. This was accompanied by use of imagery and metaphors to bolster the understanding of their symptoms, again this was attributed to a feeling of wanting legitimacy and to convey the seriousness of their illness. Of note that for those who did not have metaphors to aid with their description, they appeared to find it difficult to articulate their symptoms, *'for me it's like a*

weakness... it's almost like you're not sure if your body will carry you across the room... it's hard to describe actually, hard to articulate' P6.

3.3 Fear of negative evaluation

Alongside this, participants appeared to be fearful of negative evaluation from others, *'well you don't want to show weakness... I think other people hear it and that look comes over, that look of shock and then pity' P4.* It is also possible that participants did not want to make people aware of the illness due a fear it may not be acknowledged by others resulting in feelings of isolation. Participant 6 spoke of when she initially started participating in more activity, she believed others may judge her, *'I'm just going to have a walk in this bit of the garden and you know, so you can build it up and it feels quite safe and like, nobody's there, nobody's like watching you... it might sound crazy because I probably look really well and I think, I don't think I can make my legs move and it's horrible, horrible thing. But I think somebody might be looking at me and think, what's wrong with that women'.* Here the narrative around the lack of legitimacy of the illness again, that behaving like someone who is ill makes her 'crazy'. This may be linked to concerns the illness is 'all in their head', that she does not really have a legitimate reason to behave as she does.

Participant 2 described an occasion when she was socialising however began to feel ill and became aware of managing how she was being perceived while feeling ill, *'during the conversation I thought, I've, do you, I feel so ill, I feel terrible... so while I was chatting with my friend I've got this inner monologue*

going on in my head saying... you're alright, you're not dying... and at the same time trying to chat and act as if everything is ok' P2. This management of how others may perceive them is tiring in itself but is strongly linked to managing expectations which again contribute to feelings of isolation and fear.

3.4 Wanting understanding and compassion

As well as wanting empathy, participants, as described earlier, also wanted to do more and try different activities to see what works. When discussing the support of family members, participant 6 described the conflict between letting her do more and wanting to help manage her symptoms, *'their natural instinct is that they don't want you to do anything, they just want you to rest all the time... one of the hardest things now is getting them to actually let me do some stuff... because I can't live my life not doing things because it might have a negative impact'*. Here the narrative around a strong desire to engage in life however this was in conflict with those who want to help.

Although, this was discussed alongside concerns of engaging in activity with people who do not understand the illness. *'As long as they listen, so if I say, look I appreciate you wanting me to do this but I've got to go home and function at home as well...if I thought they weren't listening to what I was saying and not taking me seriously then I probably wouldn't go back' P2.* Here the descriptions of concern and apprehension of engaging in activity if there was fear that someone may want to keep pushing them. From previous experience this creates a belief that without allowing them to rest when needed this could cause another relapse in symptoms and undo any progress to date.

4. Small wins and flexible approach

This theme is related to descriptions relating to how participants had modified their lifestyles to manage the illness. Participants talked about strategies they had tried and tested to maintain a degree of independence however the illness still caught them out at times. They all described the importance of small incremental '*wins*' however the illness was always there and could still '*catch them out*'.

4.1 Wanting to do more but fearful symptoms may worsen

However, participants also spoke of occasions when they knew they would feel ill following activity however they believed participating in that activity was worth the cost. '*I don't want to go to bed and lie down and go to sleep because I'm still going to feel, I don't know, I know I'll still feel the same, so I still want to be present if that makes sense*' P6. The description again reinforces this desire to be more active and engage in activities of daily living. There is an acceptance that to do something they enjoy, it will come at a 'cost'. However this was directly contrasted to the fear of overexertion. '*It terrifies me, to get to a point where I'm not doing anything, I don't want to be that person, I want to go out and have a walk, it's not a big thing, but it's a big thing to me*' P2.

4.2 Consequences of doing too much

The participants in this study did not describe boom and bust cycles which are commonly cited in ME/CFS literature, nevertheless participants did describe in detail circumstances where they had done too much and the subsequent consequences of this. '*I'd been absolutely fine, I'd been walking, my legs*

weren't even aching and then it literally was, like no energy and it was the hardest thing ever just to do that five minutes back to the hotel' P4 and 'I ended up in bed for days and I couldn't, I physically couldn't move and I, and I, it terrified me' P2. Here the language of being terrified, which results in a lasting impression of doing too much.

During a period when symptoms had been particularly severe, participant 3 used language around lack of control to describe their symptoms which contribute to fear during a 'flare-up' of symptoms. *'If you imagine, like when you were a teenager and you were drunk but pretending to your parents that you weren't drunk, that's how I feel having a conversation with someone, I feel like I'm thinking about every single word and trying to hide it almost' and 'it was so weird, like I'd been drugged almost'.* The descriptions illustrate how the concentration necessary to stay awake and alert when they feel tired adding to feelings of exhaustion and can be a distraction from the ability to enjoy the present moment. This link with a feeling of forgetfulness and a difficulty in concentration.

4.3 Small wins and mini independence

Participants spoke of tasks that they viewed as their personal jobs that they liked to complete, *'you know I still try to maintain this kind of level of minute independence' P1.* These tasks were also viewed as a measure of how ill they were feeling, *'you know, and do you know what's really stupid, for me, god, a big achievement is getting in the shower and putting my makeup on. And I think, do you know what, I've done that today, that is great' P2.*

Participant 6 described the journey of small incremental improvements; however, these were not necessarily a conscious decision to achieve a certain outcome, more the desire to do more. *'I'll just look out the window, I didn't dare have a rest, I'm just going to look out the window, because I felt having a rest didn't feel very positive... that felt to me like a success, rather than, oh I'll have a rest, felt like failure... it as only recently and I thought I didn't look out the window... that was like amazing, that's marvellous, that's fantastic'.*

'just going from that point of not feeling useless... more a case of, it is what it is and almost acceptance of it... it impact on the level of mood and you know, I think that feeling of despair and depression wasn't quite as great... just feeling like by doing an awful lot less, you're still doing something' P3.

Here the importance of achieving 'something' was clearly described in the interviews and how this improved mood and produced feelings of elation. As described earlier this feeling of happiness is attributed to the re-engagement in pre-illness 'self'.

4.4 unpredictability and need for flexibility

Alongside this, participants described the unpredictability of the illness and even after planning for events where they were aware that they could be overexerting themselves their symptoms could still worsen. When asked about the importance of goal setting participant 3 stated. *'It was almost a fear of setting a target that I wasn't going to achieve, that was going to knock me*

back, impact on me negatively'. This concern over not achieving a goal and the negative impact this may have was also described by participant 6. *'Maybe I also got to the point of the fatigue getting really bad by putting a lot of pressure on myself... I'm worried if I put too much pressure on myself that I just, you know, go again'*. The fear of relapse was commonly discussed throughout the interviews. Participant 5 described the process he goes through when deciding how much activity to participate in, *'so it's up and down, there's no set two or three days, I can say if I do this today I'll be alright tomorrow or I'll work in this thing, it's pretty much wake up in the morning and say right, what do I feel like...'*

'Sometimes I can surprise myself... I mean I'm not stupid and I do it and I know, well I'm gonna pay for that because I didn't feel great doing it. But sometimes my symptoms are not horrendous and I can, myself go that little bit further, I don't know why that is' P2. Participant 2 also described the importance of planning for activity *'if I want to do something I know that for a couple of days before hand I'm gonna, you know not push myself, so I'll try and rest at home and then I can kind of gauge it'*.

4.5 It still catches me out

The ability for the illness to still catch participants out was another description across all of the interviews. Again this contributes to feeling out of control and a fear that this illness could worsen at any point. This links to feelings of isolation as people with ME/CFS have the risk of a relapse in symptoms. *'I'll suddenly be stood there, and I can't find a word... or I find that I've been*

staring at the computer screen and like ten minutes has gone and I've not done anything' P4. Following exercise P5 described the illness sneaking, catching him unawares, *'I'm hoping it's not this coming, this sneaking in and coming again' P5.*

8.6 Discussion

This qualitative study provided a detailed account of the role of physical activity for people with ME/CFS. This study is the first to use an IPA approach when exploring physical activity and ME/CFS with the inclusion of a PPI group to aid in the interpretation. People with ME/CFS described a profound sense of loss, related to their sense of identity. They described becoming increasingly isolated and unable to participate in activities of daily living which previously provided a sense of self as well as enjoyment. As participants transitioned through their illness, they demonstrated a need to bolster the legitimacy of their condition. Particularly when faced with judgement from others due to the invisible nature of the symptoms alongside isolation, which was proved to be a fundamental aspect of the illness experience. A sense of uncertainty surrounded their illness and the sudden onset of symptoms could still 'catch them out', even if they plan and prepare for activity, which made participants feel vulnerable and out of control.

Isolation was discussed across all six interviews and appear to be an important part of the participants experience, which is in agreement with other qualitative work in ME/CFS (Dickson *et al.*, 2008; Anderson *et al.*, 2012; Wilde *et al.*, 2020). A lack of social involvement was described by Larun *et al.*, (2007) who

reported in their systematic review of qualitative studies that participants described a significant negative impact of the illness on their social relationships and activities. Although, Larun *et al.* (2007) did not explore this in any further depth.

In the current study all participants discussed engaging in some form of physical activity, described by one participant as maintaining his 'minute independence'. Dickson *et al.*, (2008) stated that chronic illnesses such as ME/CFS can force drastic changes in terms of life course, particularly for roles and responsibilities, which can challenge the individual's identity. Wilde *et al.* (2020) conducted an IPA study which explored masculinity in ten men with a diagnosis of ME/CFS. Wilde *et al.* (2020) stated that throughout the participants accounts they expressed feelings of losing their sense of masculine self-worth. This was due to their inability to meet social and previous personal expectations of "being male" since the onset of the illness. Wilde *et al.* (2020) argued that these expectations seemed to be based on monolithic social representations of masculinity. As being a breadwinner who is socially, physically, and sexually potent, and emotionally and physically strong. In the current study all the male participants provided a spontaneous discussion, recalling a period prior to their illness when they took pride in "going out and working hard". In doing so, they described this as giving themselves a feeling that they had earned the right to feel tired. They discussed their role in the household including DIY tasks and participating in family roles such as cooking and walking. Which would support findings by Wilde *et al.* (2020) that this

illness may have resulted in a sense of loss in relation to their role within the family unit.

Loss of identity has been reported in several qualitative studies in ME/CFS (Larun *et al.*, 2007; Anderson *et al.*, 2012; Pemberton and Cox, 2014). Larun *et al.* (2007) reported that people with ME/CFS described feeling marginalised as their lifestyle became more passive, which led to loss of relationships with significant others and transformation of identity. Larun *et al.* (2007) furthered this by arguing that a lack of identity was sustained by the person feeling significantly ill 'yet feeling blamed, mistrusted, dismissed and morally judged by everyone', which was supported by Gilje *et al.* (2008). A subsequent lack of organic explanation led to the person's illness experience being denied (Larun *et al.*, 2007; Gilje *et al.*, 2008). This resulted in marginalisation, which Wilde *et al.* (2020) described as being erased from the social world, and resulting in perceived social marginalisation. Dickson *et al.* (2008) further argued that people with ME/CFS may internalise scepticism and even begin to question the authenticity of their condition. Dickson *et al.* (2008) argued that scepticism contributes to a disruption in the individual with ME/CFS life and may even heighten the crisis of self.

The participants in the current study described going through an initial period of 'battling' with the condition which is not commonly cited in other chronic health conditions. Ansari *et al.* (2014) interviewed 17 participants about their diagnosis with COPD and reported that participants accepted their diagnosis, although this sample already had a number of co-morbidities prior to

diagnosis. It is theorised that this process of 'battling' maybe a unique characteristic of ME/CFS. Alongside this the participants describe the event of becoming ill as a descent, that they would use strategies to reduce activity such as taking sick leave from work and resting. However, these strategies were unsuccessful and their symptoms continued to worsen. Larun *et al.* (2007) reported that getting a diagnosis was described as the single most important event by those with ME/CFS. Brown *et al.* (2017) described this as a liminal state where people with ME/CFS were often feeling very ill, but with a diagnosis that they felt was not taken seriously; outside the grid of intelligibility provided by more established illnesses, and without a treatment which is generally believed to be helpful or consistently available.

This period could be considered a 'no-man's land', a time of transition. Where people with ME/CFS are in a period of turmoil. Not knowing what is wrong but, also not knowing how to put it right, or what this period will transition into and therefore continued to struggle in this liminal state. The diagnosis however, may have given them a sense of direction to aid in leading them out of liminality. This was described in Dickson *et al.* (2008) who described the transformation of identity into 'otherness': the individual experiences life outside the 'normal' self and their 'normal' world. Although only a partial transformation, where the individual partly belongs to their life prior to illness and partly to a life with (or after) the onset of the condition (Dickson *et al.*, 2008).

However, for those with ME/CFS they entered a new liminal state required to manage dilemmas such as how to construct and communicate a recovery in the absence of recognised medical or lay criteria (Brown *et al.*, 2017). Brown *et al.*, (2017) stated that participants in their study, used engagement in what they considered to be normal life as evidence of a recovery. Pemberton and Cox (2014) stated that with ME/CFS, there appears to be a societal perception of those who experience the illness; with a historical stigma around perceived laziness and activity-avoidance.

However, Brown *et al.* (2017) and Pemberton and Cox (2014) demonstrated that activity avoidance in ME/CFS is not the case. Brown *et al.* (2017) argued that the people with ME/CFS in their study were 'pro-active agents', urgently seeking recovery and this was reported to be consistent throughout their data. Furthermore, they found that people with ME/CFS were willing to adapt their lifestyle to eradicate anything that may be regarded as contributing to the illness. However, the current study develops this further identifying that the uncertainty around the illness inhibits the ability to plan which leads to frustration and apprehension.

Many of the participants in the current study discussed creating their own informal recovery programme that was flexible and contained multiple options of duration, with distance being the primary method to differentiate. This was supported by Brown *et al.* (2017) who stated in their study of liminality in ME/CFS recovery that the recovery process was generally described in terms of individual effort and responsibility. To some extent, participants had to

formulate their own methods of recovery and meanings for the process (Brown *et al.* 2017). The participants in the current study all described wanting to do more, however this was not just in relation to exercise and instead involved in more general activities and socialising. As with previous studies, the data demonstrates that any inability to participate in activity appeared to be due to the illness and not due to motivational factors.

The participants in the current study would use timing and distance as a measure of 'wellness', for example, I cycled for 20minutes, I walked to the second lamppost. This use of time and distance for people with ME/CFS maybe related to a lack of an objective measurement of being 'ill' and therefore, no objective measurement of being 'well'. Indeed, feeling worse or feeling better are concepts subjective to each individual. This was demonstrated by Brown *et al.* (2017) which argued that the process of recovery in ME/CFS is a process of measurement and timing. How many hours of exercise can be sustained, how many days of work, or how many lengths of the swimming pool. Brown *et al.* (2017) further argued that many of the activities, such as work, tennis or dancing are fundamentally social, involving other people integrating into 'normal' social structures. An inability to participate in these activities may be linked to a loss of self. It may be of note that participating in some form of activity, including social activities resulted in an improvement in mood for some of the participants in the current study. This improvement in mood may be interlinked to regaining a sense of self and a degree of some control. It is therefore feasible that a form of activity management may be effective in improving mood in people with ME/CFS.

Wilde *et al.* (2020) identified that in their study of men only, physical activity and sports were an important aspect of their identity which had been lost or seriously diminished due to ME/CFS. In the current study none of the female participants discussed 'exercise' in the same way as the male participants who described a 'want' and 'desire' to exercise. However, the female participants described wanting to engage in more societal activities, going bowling, walking the dog with a partner, going on holiday. This maybe a reflection of the individuals who were interviewed however this highlights the importance of individualised goal setting in any intervention and that structured exercise may not be appropriate for all.

There are a number of strengths to this study. The work is novel as it offers a new perspective in this population using an IPA approach. Further still, the use of a PPI group increases the credibility of the interpretations which are linked to illustrative quotes. During the PPI process all emerging themes were supported which provides support for the interpretations. The work was peer reviewed by different professionals with a range of backgrounds and specialties which provides a breadth of insights to the analysed data.

A limitation of this study was the recruitment strategy that was used. In this study the primary researcher made no direct contact with participants until after they had phoned or emailed themselves. A more effective method may have been for the gatekeepers to ask if the primary researcher could speak to them about the study. A purposive sampling approach may have been a more effective sampling strategy and in line with the chosen methodology. The

sample size for this study is small however it is consistent with the approach used (phenomenology), but the depth of the data is dependent on the ability of participants to articulate their experiences which can be difficult. The participants in this study were self-selected and therefore the results are not meant to be generalisable to other populations although they may resonate. Work history and educational level was not collected in this study however may have provided a greater description of the sample.

8.7 Conclusion

In conclusion those who participated in this study were actively engaging in physical activity and some were engaged in exercise and this was discussed alongside a desire to be more active. However, being more active was not just structured exercise or walking, instead a desire to engage more socially. This appeared to be discussed alongside feelings of isolation and feeling a loss of previous roles. When goals were achieved this appeared to result in an improvement in mood which may have been associated to pre-illness identity. However, the improvement in mood only lasted for a short period. It may be useful to support those with ME/CFS to participate in a greater amount of tasks/ activities which are important to themselves. The findings add weight to the unpredictability of the condition and need for flexibility.

Summary of chapter 8

This study of 6 people with ME/CFS (3 male, 3 female) provides an in-depth view of their experiences. Of note was the importance of ensuring that tasks or activities had meaning to the individual, and that this may be linked to mood, although this is only based on a limited sample of individuals with the condition. It was also of note that for a number of participants they were not necessarily interested in participating in exercise, instead a broader range of activities. The importance of understanding the unpredictable nature of the condition also appears to be an essential aspect of this illness. The participants in the study also appear to describe different stages of their illness and this may provide an insightful area for future study.

Chapter 9: The development of a physical activity intervention for the management of symptoms and activity levels in people with ME/CFS

9.0 Introduction

It has been well-established that overexertion in ME/CFS causes a worsening of symptoms commonly referred to as post-exertional malaise (PEM) (Ghali *et al.*, 2020; Hodges *et al.*, 2020). In support, there is now a growing body of evidence that this acute worsening of symptoms following overexertion may be objectively measured using exercise provocation studies (Chapter 6). These studies appear to demonstrate a leftward shift in ventilatory threshold in the second of two maximal tests separated by 24 hours (Chapter 6). While mechanisms such as mitochondrial dysfunction (Blomberg *et al.*, 2018) and immune function abnormalities (Ghali *et al.*, 2020) have been theorised as potential mechanisms for PEM, there is currently no clear explanation for the mechanism(s) involved in this process.

In chapter 8, the interviewees described wanting to be more physically active, and spoke of strong feelings of isolation and a desire to engage in activities of daily living; specifically wanting to participate more socially. Of particular note was the evidence in chapter 8 that if people with ME/CFS are able to participate in activities which had importance to themselves, this may also produce an improvement in mood. This may in turn allow them to achieve a greater level of activity. However, there is little evidence to suggest this approach would be curative and instead would be a long-term strategy to

manage their illness. It should also be noted that even if levels of activity are increased and symptoms are managed, the risk of exacerbation of symptoms and resulting PEM may still be a factor. Therefore, any intervention would need to be flexible enough to account for this unique characteristic of the illness (Chapter 8).

Currently exercise programmes in ME/CFS (known as graded exercise therapy (GET)) are implemented with the underlying theory that the illness is perpetuated by reversible physiological changes of deconditioning and propagated by avoidance of activity (White *et al.*, 2011). This deconditioning, alongside an increased perception of effort, leads to further inactivity (White *et al.*, 2011). Supporters of this model claim that a belief in an organic component of the illness would reduce the likelihood of a successful treatment outcome (Clark and White, 2005). However, in light of the evidence in Chapter 6 of this thesis, alongside evidence that GET in ME/CFS may only be effective for a small number of people with ME/CFS (Geraghty *et al.*, 2019a) and may be harmful to some (Vink and Vink-Niese, 2018), evidence does not appear to support the cognitive behavioural model as an explanation for all of the sustaining factors of the illness. Therefore, the development of a physical activity intervention based on the assumption that PEM is a physiological symptom of overexertion in ME/CFS is explored.

9.1 Aims and objectives

The aim of this chapter is to provide an overview of a proposed physical activity intervention for those with ME/CFS.

The primary aims of the proposed pilot study are to assess the utility of the proposed primary outcome measures. The primary outcome for this study is total physical activity energy and physical activity intensity. Data will be obtained on variability of the outcomes to inform sample size planning for a subsequent larger trial, and to examine participant preference effects that may influence recruitment and intervention compliance in any future large trial. Additional information is required on recruitment and retention rates, generally. As a secondary outcome, symptom levels will also be assessed to evaluate how well symptoms are being managed during the intervention.

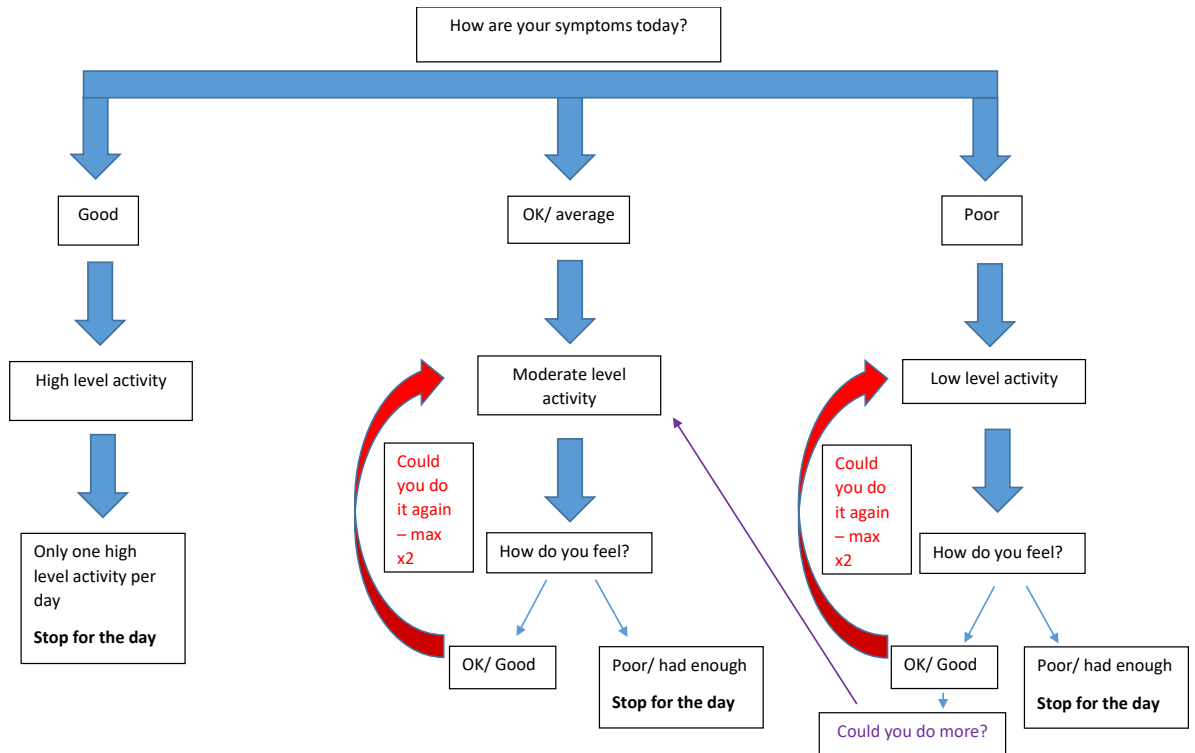
Management of symptoms and physical activity levels are defined for the purposes of this study as:

1. Assisting those with ME/CFS to manage their illness by minimising significant fluctuations in symptoms (or stabilising symptoms); that is, reduce significant relapses in symptoms or reduce the occurrence of boom and bust cycles.
2. Increasing physical activity levels in people with ME/CFS without causing a substantial worsening of symptoms, which may include; muscle weakness, muscle stiffness, pain, dizziness, headache, cognitive impairment, sleep disturbances and PEM (Goudsmit *et al.*, 2012).

9.2 Physical Activity Intervention

The intervention is designed to increase the level (frequency, duration, or intensity) of physical activity in people with ME/CFS in a way that allows flexibility for the intensity and/ or duration of activity depending on how an individual's symptoms are on a given day. The intervention would be an individualised physical activity programme with specific activity tailored for each person. Participants will be asked to consider their symptoms each day and then choose an appropriate level of activity accordingly. This approach differs starkly from traditional GET programmes which encourage participants to partake in the required activity level irrespective of their symptoms (Clark and White, 2005), although it is acknowledged that GET research studies do report recommending participants rest if there is a significant worsening of symptoms (Wallman *et al.*, 2004; Broadbent and Coutts, 2016). The proposed intervention in this chapter would allow participants to select the activity level which they believe they can achieve on any given day. This would also allow for participants to reduce activity levels to prepare for a task whilst still having a goal for that day. A sketch of the proposed intervention is shown in Figure 9.1.

Figure 9.1; Proposed intervention flow chart



9.3 Theoretical underpinnings of intervention

Based on a synthesis of previous chapters and existing literature on the topic of physical activity and ME/CFS the following theoretical assumptions are applied to the development of the proposed intervention. Firstly, there are those with ME/CFS who want to participate in more physical activity and want to engage in more tasks of daily living (Chapter 8). However, the illness can be unpredictable, and any intervention must allow for daily fluctuation in symptoms (Chapter 8). Secondly there may be a physiological component of the illness; therefore, it is recognised that the cognitive behavioural model of ME/CFS which underpinned GET may no longer adequately explain all components of the illness (Chapter 6). Thirdly, mood and emotional stress

contribute to symptoms and therefore any programme should not neglect cognitive components of the illness (Chapter 2 and Chapter 8). If the stressor (cognitive, emotional, or physical) is too great this will cause a relapse in symptoms (ICC 2011; IOM 2015) and therefore any progression in activity should be monitored and flexible. Finally, engagement with activities that are meaningful to the individual may help improve mood which may also aid in symptom improvement. However, any improvement would be short term and would need to be maintained and managed. An improvement in mood may not be an indicator of the intervention reversing negative illness beliefs. Instead it might reflect the consequences of the individual engaging in activities which bring enjoyment and possibly some connection with their life prior to being ill.

Enjoyment of a task, its meaningful nature, and giving control to the individual have been shown to be key concepts in engagement with rehabilitation/lifestyle change with adults (Dekker *et al.*, 2020). If an individual can select the activity that is meaningful for them, this can enable a return of their perceived role and contribution within a relationship (Dekker *et al.*, 2020). This holistic approach to rehabilitation is important for motivation and enables clearer prioritisation of tasks which are meaningful to the individual (Patil *et al.*, 2019).

9.4 Developing the Intervention

9.4.1 The development of the Initial Concept

French *et al.* (2012) stated that the design of an intervention requires a systematic approach with a strong rationale for design and explicit reporting of the intervention development process. The initial idea was developed for the intervention during the qualitative study (chapter 8) data collection period. During the data collection it was noted that participants would often participate in different activities depending on how they felt on a day to day basis. There were some key points to note, firstly that those interviewed had a number of different levels of activity. They would choose the mode, intensity, or duration of activity they would participate in each day. Sometimes this decision making was by choice, however it was often through necessity due to competing demands. Secondly, unlike the theory of GET in CFS/ME, most people with ME/CFS used their overall feelings of illness severity to indicate how much they could do that day.

Alternatively, the volume and intensity of activities may require planning, such as resting knowing that they intended to complete a task at a later period that would require some degree of energy reserves. It is noted that some interviews took place following Christmas and those interviewed over this period discussed reducing activity levels to help manage their symptoms during this time. Participants also spoke of 'trying out' how they felt. For example, one participant spoke of how they may take a short walk in the garden and if that was manageable, then they may feel better than originally thought and may

be able to do a little more. This option of allowing more activity, whilst capping the overall level of activity, provided interesting insight and was incorporated into the programme.

Following this initial idea JF, AB and GA discussed the initial ideas for the programme. Originally it had been discussed to have a traffic light system and this idea was developed further to the programme noted below. Through further discussion AB discussed the use of metabolic equivalents (METs) as a measure of activity and this led to the concepts of providing options as opposed to traditional exercise activities. Discussion with the supervisory team continued and a number of ideas were discussed and refined for the intervention noted below.

9.4.2 Patient Advisory Group

As discussed in chapter 8, patient and public involvement (PPI) was sought through the development of the Teesside University ME/CFS patient advisory group (PAG). Unfortunately, the majority of PPI discussion for this intervention was due to commence in March 2020; however, due to the COVID-19 global pandemic this process was stopped, as no face to face contact could be made during this period. Moreover, as the individuals involved with this group were either people living with ME/CFS or health care professionals working directly in the health care environment the decision was made by JF to pause any PPI group work until the pandemic had slowed. This was primarily to ensure that those with the illness who may be concerned about COVID-19 were not

receiving extra communications from JF which could exacerbate symptoms during an already highly stressful period. It is acknowledged that the lack of PPI is a limitation, and it is recognised that a full PPI process will need to take place before this intervention is taken forward.

An initial PPI process had taken place; however, concerning the general concept of the intervention to get an indication of the feasibility of the project. All those who were consulted, including people with the illness and health care professionals, believed that the intervention was promising; however, as noted above these discussions did not explore the specifics of the intervention. One health care professional did highlight that they felt it was important that cognitive stress was considered as well, and that the programme did not just focus solely on physical activity. This feedback was incorporated into the programme. Feedback was provided from 3 health care professionals (2 physiotherapists and 1 occupational therapist), 1 sport and exercise scientist with expertise in exercise and physical activity programme development, 1 psychologist and 3 people with ME/CFS. All stated that the intervention had potential to assist people to manage their activity levels and had the potential to aid in increasing physical activity levels in people with ME/CFS. The intervention was also discussed in detail with AB and GA.

9.5 Behavioural Change

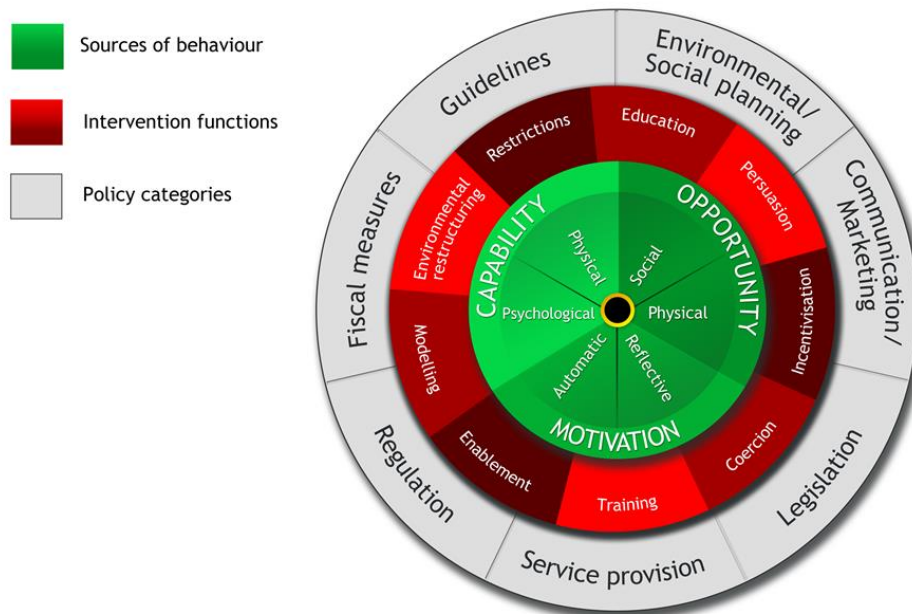
Evidence indicates that for an intervention to be successful it should be underpinned by appropriate theory (MRC, 2006; Prochaska, 2008), as this can

aid in establishing the core components (or '*active ingredients*') of an intervention (Michie *et al.*, 2009b). Using appropriate behavioural change theory when developing interventions such as the current proposed study, requires an understanding of the mechanisms by which the intervention causes behavioural change (Michie *et al.*, 2009b). In a systematic review of behaviour change interventions it was reported that where effects are found it is often unclear which behaviour change processes are responsible for the observed changes, and only a minority of the frameworks assessed demonstrated coherence or linkage to a model of behaviour (Michie *et al.*, 2009b). To aid this process, Michie *et al.* (2011) developed the behavioural change wheel (BCW) which is described as a theory- and evidence-based model for characterising and designing behaviour change interventions (Seppälä *et al.*, 2018). The BCW is described as a comprehensive and coherent framework that links interventions to an overarching model of 'behaviour system' (Michie *et al.*, 2011).

The BCW requires intervention designers to consider the conditions which are internal to individuals and the social and physical environment, variables and context that are important to the specified behavioural target to be achieved (Michie *et al.*, 2011). The BCW is comprised of three layers. The inner layer identifies sources of behaviour that may be beneficial to target with an intervention (Michie *et al.*, 2014). Surrounding this layer are the intervention functions which can be identified following the COM-B analysis. The outer layer identifies types of policy which may be beneficial to deliver the

intervention functions. For the purpose of this proposed intervention, policy types will not be explored, a diagram of the BCW can be seen in figure 9.2.

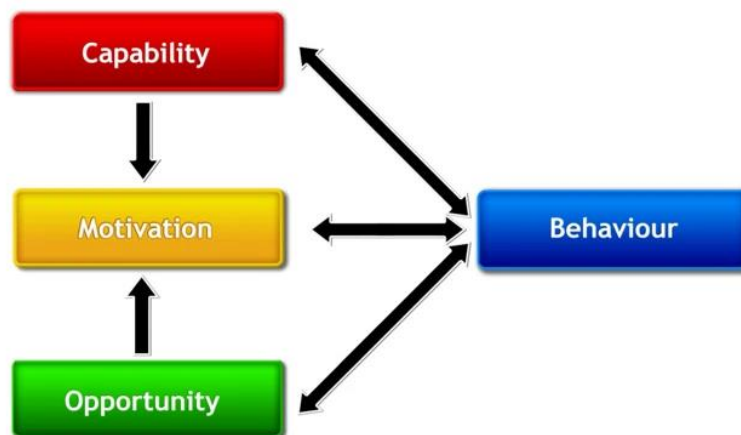
Figure 9.2; Behavioural Change Wheel taken from Michie *et al.* (2011)



To aid this process a modified version of Michie *et al.* (2014) behavioural change intervention design process was used. This was modified to include 7 stages instead of 8, as at this stage in the development of the intervention the type of policy category was not considered. Seppälä *et al.*, (2018) argued that for behaviour change interventions to be effective they should focus on components that are most likely to influence the target behaviour of the target population in a specified context. To identify the specific target behaviours the COM-B tool was utilised: capability (C), opportunity (O), motivation (M), and behaviour (B) (Seppälä *et al.*, 2018). Seppälä *et al.* (2018) stated that according to the COM-B model there are three factors necessary for a

specified behaviour change. Capability is described by Michie *et al.* (2011) as the psychological and physical capacity of an individual to engage in a specific activity. Opportunity was described as factors that exist outside the individual that allow the behaviour to be possible (Michie *et al.*, 2011). Motivation was described as cognitive processes that energise and direct behaviour (Michie *et al.*, 2011). However Michie *et al.* (2011) state that this is not just in relation to goals and conscious decision-making, but also includes habitual processes, emotional responding and decision-making. An overview of the COM-B model can be seen in Figure 9.3. The Theoretical Domains Framework (TDF) was applied in line with the recommendations of Michie *et al.* (2014). The TDF is comprised of 12 domains which provide a framework of potential barriers to change and of potential intervention components.

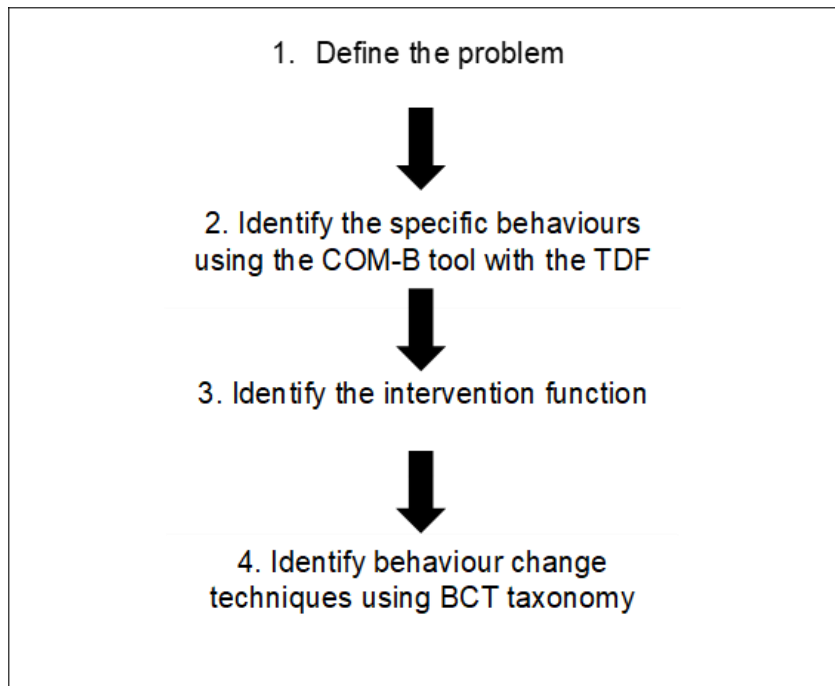
Figure 9.3; The COM-B model of behaviour taken from Michie *et al.* (2011)



Following this, the intervention functions were identified and the specific behaviour change techniques (BCT) identified as recommended by Michie *et*

al. (2014). An overview of this process can be seen in Figure 9.4 and Table 9.1.

Figure 9.4; Summary of main stages utilised in identifying behavioural change techniques for the proposed intervention



COM-B – capability, opportunity, motivation, behaviour. TDF - theoretical domains framework. BCT – behaviour change techniques.

There are some reported limitations of the BCW approach. Seppälä *et al.* (2018) stated that the BCW was useful for the assessment of individual level interventions but has limitations in describing mid-level interventions conducted in organisations, specifically when considering changes in organisational strategy, culture, or leadership (Seppälä *et al.*, 2018). Nevertheless, as the current intervention is designed for individual level changes in behaviour this limitation is not important herein. Furthermore, French *et al.* (2012) stated that there is currently no systematic basis for

determining which among the various theories available predicts behaviour or behaviour change most precisely, or which is best suited to underpin implementation research.

Table 9.1; Behaviour change techniques identified through BCW process

COM-B	Barrier	TDF	Intervention function	Behavioural change technique
Psychological capability	Knowledge	Lack of knowledge of proposed intervention	Education	Information about how to perform behaviour Feedback on behaviour Self-monitoring of behaviour
Psychological capability	Skills	Insufficient knowledge of programme	Training	Instructions about how to perform the behaviour Feedback on the behaviour Self-monitoring of the behaviour Bio-feedback (heart rate)
Psychological capability	Knowledge	May have insufficient knowledge and experience to set realistic goals	Enablement	Goal setting (outcome) Goal setting (behaviour) Review outcome goals Review behavioural goals Self-monitoring of outcomes of behaviour

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Reflective motivation	Belief about consequences	May believe that increasing activity may worsen symptoms	Education	Information about others approval Self-monitoring of outcome of behaviour
BCTs identified through BCW process to incorporate into the intervention Information about how to perform behaviour Instructions about how to perform the behaviour Feedback on behaviour Self-monitoring of behaviour Bio-feedback Goal setting (outcome) Goal setting (behaviour) Review outcome goals Review behavioural goals Information about others' approval				

Michie et al. (2009a) stated that evidence for physical activity interventions indicated that self-monitoring of behaviour was associated with improved effectiveness, especially when combined with the following four elements; intention formation, specific goal setting, feedback on performance, and review of behavioural goals. Michie et al. (2009b) further stated that few published intervention evaluations refer to formal documentation describing the content and delivery of an intervention and are seldom reported by researchers or practitioners in enough detail to replicate them. To further aid with providing adequate description for replication, the Consensus on Exercise Reporting Template (CERT) statement (Slade *et al.*, 2015) has been applied to the description of the intervention.

9.6 Key methodological features of proposed study

9.6.1 Initial training and education

Performance is a function of both ability and motivation, and successful achievement of goals is also dependent upon having the necessary task knowledge and skills (Locke and Latham, 2006). Participants will initially be asked to attend a session where the approach to the intervention will be explained. Participants will be provided with information and training on the principles of pacing (section 9.6.2) and guidance on how to implement this. Participants will be introduced to the outcome measures and shown how to use these, given the opportunity to practice with these and given the opportunity to ask any questions. Participants will also be made aware that a PAG was involved in the development of the intervention. A second meeting will take place after the lower level of activity has been defined for each individual to discuss goals and action planning.

9.6.2 Setting the lower level of activity

The lower level of activity will be assessed using the pacing methods described by Jason *et al.* (2013b) and Goudsmit *et al.* (2012). Pacing is defined as an approach to illness management where those with ME/CFS are encouraged to be as active as possible within the limits imposed by the illness (Goudsmit *et al.*, 2012; Jason *et al.*, 2013b). Goudsmit *et al.* (2012) stated that pacing requires the individual to determine a level at which they can function but which does not lead to a marked increase in fatigue and other symptoms for up to five days (Goudsmit *et al.*, 2012). Typical cues that those with

ME/CFS have exceeded their 'limits' include the onset of muscle weakness, muscle stiffness, pain, dizziness, headache and PEM (Goudsmit *et al.*, 2012). Depending on the nature and severity of the symptoms, participants can either stop and rest or change to an activity involving a different muscle group, or both (Goudsmit *et al.*, 2012).

Goudsmit *et al.* (2012) reported that systems which allow an individual to assess their own capability may include the use of a fatigue rating scale used each day on a visual analogue scale (VAS), where 0 means 'no fatigue' and 100 means 'extreme fatigue'. Goudsmith *et al.* (2012) also suggested that perceived energy can be given a score from 0 representing 'no energy at all' to 100 denoting 'energy similar to that when well'. Finally, a score could assess expended energy, where 0 means 'no energy expended' and 100 means 'all energy used up'. In the current intervention it is proposed that participants will be asked to maintain an activity diary. Alongside this, participants will be asked to record their energy levels as described by Jason (2008). The aim will be to find an optimum level where participants are able to achieve a degree of activity while maintaining some amount of perceived energy. Importantly, the aim should be to minimise any signs or symptoms of PEM. Over the two-week period the aim would be to achieve an optimum level of activity and perceived energy for the individual. A two-week period is proposed; however, this process may take longer for some individuals.

Exploring the Relationship between Physical Activity and ME/CFS

Before introducing any other levels of activity participants will be asked to maintain the lower level of activity for 2 weeks. During this time participants will be asked to record their symptoms and what activity they have participated in and how their ME/CFS symptoms have been during this period. If at the appropriate level, it would be assumed that participants will be able to achieve this level of activity without any significant worsening of symptoms. Setting this baseline level of activity will be fundamental to the success of the programme. It may also be the case that some individuals are already participating in some physical activity and therefore this stage may be used to highlight and explicitly acknowledge that the participant is already involved with a degree of physical activity.

This lower level activity could also be described as a 'safety activity'; that is, a realistic and achievable level of activity. During the interviews in chapter 8, it was noted that some participants stated they would be reluctant to engage with the idea of an exercise programme as they believed that unsuccessful engagement in the programme may result in feelings of failure and therefore they would avoid beginning a programme of this type. The low activity level would be set at a level that participants know they could achieve and may even be a level they are already achieving on a daily basis. Therefore, the aim under these circumstances would be to demonstrate to the individual that they are already achieving a goal using the programme, thus increasing feelings of competence, capability, and motivation.

Importantly, the programme is aimed at increasing activity levels and not specifically exercise. Therefore, the programme is applicable to those with differing severity of symptoms and the activities can be tailored accordingly. For example, showering may be a low-level activity, showering and washing own hair moderate, and showering, washing own hair and drying own hair a high-level activity. Walking down and back up a flight of stairs may be high-level activity for another, while somebody else's aim may be to complete a 5k run. This high degree of flexibility would potentially allow application to a broader group of those with the condition, especially with a primary aim in supporting activity rather than improving symptoms (although an improvement in symptoms would be a positive outcome). Of note, this approach could also be adapted to allow an individual to include cognitive tasks in the programme. A final point to consider is that Goudsmit *et al.* (2012) reported that pacing requires a large amount of behavioural change and clearly this initial stage of creating the boundaries for the lower levels of activity requires a high degree of education, training, and support.

9.3.3 Goal Setting and reviewing of goals

The first principle in any treatment is to help individuals set realistic goals (Prochaska, 2008). A goal, described as the object or aim of an action (McEwan *et al.*, 2016), and the process of setting goals facilitates behaviour change by guiding individuals' attention and efforts, and increasing persistence towards obtaining a specified level of proficiency (McEwan *et al.*, 2016). Locke and Latham (2006) stated that specific goals lead to a higher

level of task performance than vague or abstract goals such as “do one’s best.” Therefore the goals will be specific to each individual such as baking with a grandchild, shopping for ingredients, or following a recipe. Task goals with outcome success criteria established by the individual would lead to a greater likelihood of achievement, increased self-efficacy and greater adherence (Picha and Howell, 2018). Importantly, a number of authors have highlighted the importance of self-efficacy (task-specific confidence; Locke and Latham, 2006) in relation to goal setting (Michie et al., 2011; McEwan et al., 2016).

A discussion can then take place with the participants about their specific long-term goals. Long-term goals can be considered and broken down into short-term goals enabling the next level of activity to be set. It is believed that this process would involve some trial and error, especially when beginning the programme. However, the level should be appropriate in that it involves more activity than the previous level and causes no significant worsening of symptoms. To begin with, the participant should be able to achieve low and moderate levels of activity albeit the moderate level requiring more physical/cognitive energy. McEwan *et al.* (2016) reported in a meta-analysis of 45 studies that when goal setting, alongside providing feedback on goals, incorporating strategies to achieve goals resulted in significant effects in favour of the intervention. Interventions appeared to be most effective when goals were set in relation to daily physical activity (McEwan *et al.*, 2016). Initially, goals would be reviewed with support of a practitioner; however, the

long-term aim would be to provide the skills necessary for an individual to self-assess and self-manage their own activity levels and goals.

9.6.4 Flexibility of activity choices

To allow for flexibility within the intervention instead of stating single activities or asking participants to take part in other activities, participants will be asked what activities they would like to do and then metabolic equivalents (METs) will be estimated for each activity. Using The Compendium of Physical Activities website:

<https://sites.google.com/site/compendiumofphysicalactivities/Activity-Categories/home-repair>, participants can then be asked to try and achieve a given duration of activity at a given MET level. By using this method participants can be given a number of activities as the level provided by the MET indicates the level of intensity along with a set duration which is negotiated with the research team.

9.6.5 Feedback and self-monitoring of behaviour

Keeping a physical activity diary to record daily activity type, intensity and duration alongside an overall symptom severity scale will be used. Rating of perceived exertion (RPE) has been shown to be a practical and valid tool for monitoring and prescribing exercise intensity (Scherr *et al.*, 2013). Tang *et al.* (2016) also demonstrated that a diary-led and self-regulated model using RPE can help guide exercise intensity in everyday clinical practice among patients with heart disease. Differentiated RPE (DRPE) has been shown to be effective

in conditions such as cystic fibrosis (Gruet *et al.*, 2018). DRPE can be measured as overall body feelings of exertion, or differentiated feelings reflecting respiratory and metabolic functions arising from the chest and alterations in energy production, as well as peripheral and skeletal muscle (Bolgar *et al.*, 2010). The use of DRPE has been shown to be effective in quantifying internal load in professional rugby players (McLaren *et al.*, 2017). However, to date this has not been assessed in ME/CFS, therefore its use would need to be validated before using in this proposed study. Nevertheless, the use of DRPE may assist in providing autonomy to the participants by allowing self-regulation of exercise intensity and should promote long-term adherence to physical activity through the development of a more intrinsically motivated physical activity behaviour (Gruet *et al.*, 2018).

Other methods that could be developed in the future are the use of an app on a mobile device. This could provide a list of appropriate activities and participants could upload the type and duration of activity as well as their total symptom rating (or this could be broken down into symptom type). Feedback could then be provided instantly in graphical format providing information about activities each day and week in relation to targets alongside symptoms severity data. This would allow participants to identify their progress. It would also allow monitoring of symptoms in relation to activity to ensure these are at the appropriate level and not causing an exacerbation of symptoms.

9.6.6 Progression

The process of progressing the programme would need to be agreed with the participant before being carried out. In essence, progression would mean the programme shifts to the right; that is, the moderate activity becomes the new low activity, high becomes the new moderate activity and a new high activity is defined. This process would occur when the participant felt ready to progress and this would be negotiated with the practitioner supporting the individual.

9.6.7 Assessing adverse events

Reporting of harms in RCTs has received less attention than reporting of efficacy and effectiveness and is often inadequate (Ioannidis *et al.*, 2004). The recommendations made by Ioannidis *et al.* (2004) have been used to develop the overview of adverse events. Table 9.2 provides a summary of the terminology used in this section.

Table 9.2; Definition of adverse events terminology

Term	Definition
Adverse events	Harmful events that occur during the trial however may not be related to the intervention (i.e. consequence of underlying health condition).
Adverse reactions	Harmful events that are a consequence of the intervention and there is a well-established causal link to the tested intervention.
Harms	The totality of possible adverse consequences of an intervention or therapy. They are the direct opposite to benefits, against which they should be compared.

Serious adverse events	Adverse events which threaten life or function. Clark <i>et al.</i> (2017) reported that this could include hospital admission, increased severe and persistent disability or self-harm. Or when life was threatened or when intervention was required to prevent one of the events noted.
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Information taken from Ioannidis *et al.* (2004)

For the proposed intervention it is essential that adverse events are recorded and reported in any evaluation. During the recruitment stage the possibility of adverse events will be clearly explained to the participants in the participant information sheet, consent form, and any discussions with participants with an aim of priming participants and improving the reporting of adverse events (Ioannidis *et al.*, 2004). It is proposed that adverse events of all the included participants will be recorded, including both anticipated vs unexpected events.

A '*proactive*' investigation of adverse events will be conducted using a questionnaire to participants about possible events during the intervention and possible causes. Recording of adverse events will take place up to 2 weeks following the end of the post-test, as this will have been an adequate time period for any adverse reaction to the intervention to have taken place. Participants who drop out of the study will also be followed-up and attempts to ascertain information relating to reasons for drop-out will be assessed. Those who drop-out will also be provided with a copy of the adverse events questionnaire. Data will be reported for each specific event in each arm of the RCT and the aim is to report the number, type and severity of events. Absolute risk for each type of adverse event, such as frequency of incident will be

recorded and reported separately in relation to severity of event (Ioannidis *et al.*, 2004).

9.6.8 Outcome Measures

The MRC (2006) stated that a crucial aspect of the design of an evaluation is the choice of outcome measures. The primary outcomes for this study will be activity measured using Actiheart (Cambridge Neurotechnology Ltd, Cambridge, UK), which is a device employed to collect physical activity energy expenditure and uses synchronized accelerometry and heart rate (Thompson *et al.*, 2016). This device will allow for the assessment of sedentary, moderate, and vigorous physical activity, total physical activity energy expenditure and physical activity level (PAL; a ratio of total energy expenditure to resting metabolic rate). It will also examine day-to-day variability in activity intensity.

A measure of overall symptoms would also be assessed, however further evaluation of the validity and reliability of the specific tool will need to be conducted. Other methods to be assessed are visual analogue scales for pain and fatigue (Nacul *et al.*, 2018), however, further assessment of this tool is required. The secondary outcomes include perceived fatigue assessed using the fatigue severity scale (FSS) and quality of life (health status) using the SF-36 questionnaire. Both the FSS and SF-36 demonstrate good validity and reliability in people with ME/CFS (Jason, 2005).

9.7 Evaluating the intervention - piloting and feasibility

MRC (2006) stated that the feasibility and piloting stage involves assessing acceptability, estimating the likely rates of recruitment and retention of participants, and the estimation of appropriate sample sizes for a future larger trial. They state further that evaluations of interventions are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment and retention and smaller than expected effect sizes (MRC 2006). When assessing the impact of an intervention, it is important to consider how the intervention will work in everyday clinical practice (MRC 2006) or the home setting of the clinical group. Secondly, the MRC (2006) guidance stated that it is essential to understand what the '*active ingredients*' of the intervention are and how it exerts any effect to try and develop a better understanding of the causal mechanism. To inform a subsequent larger 'definitive' trial, a single blind parallel groups external pilot randomised controlled trial (RCT) is proposed. Participants would initially be recruited using the DePaul CFS questionnaire, as well as assessment using the ICC (2011) and IOM (2015) criteria for ME/CFS. The comparison group for this study would be treatment as usual (TAU).

When designing randomised controlled trials (RCT) it is important to assess whether participants are willing to be randomly allocated to either a treatment or control group. If participants have a strong preference to a particular group and then are allocated to what they perceive to be the 'wrong' group this can result in the phenomenon known as resentful demoralisation (RD) (Torgerson

and Torgerson, 2008). This in return may result in non-compliance with an intervention or may increase the drop-out rate (Thomas *et al.*, 2004). As well as introducing bias in terms of participants non-compliance with the specific intervention there is also the risk of psychological bias with controls underperforming impacting on the internal validity of the study (Bower *et al.*, 2005). Traditionally preference effects were addressed through the use of blinding; however, when studies are assessing the effectiveness of interventions where blinding is not possible this could introduce the possibility of RD (Bower *et al.*, 2005). Howard and Thornicroft (2006) discussed this issue further highlighting that RD may be a result of factors such as the perception of the individuals, previous experiences and personal preferences, as well as the impact of social stigma.

In the proposed pilot RCT preference effects will be explored qualitatively. Evidence of strong preference effects will inform the design and methods in any subsequent definitive RCT, including providing evidence-based information during recruitment to improve informed decision making and facilitate participation in the trial (Mills *et al.*, 2011). Other methods to address preference effects in RCTs include randomly allocating those who do have not preferences to groups and then those with a preference are allowed to choose which group they wish to be allocated to (Bowers *et al.*, 2005). However, by not randomly allocating to groups this can have a negative impact on the internal validity of a study as unknown confounding variables may not be controlled for (Ajetunmobi, 2002) and may limit the ability to identify true causal effects.

It should also be noted that if patients decline from entering a trial because of the perceived risk of being allocated to the 'wrong' group this could impact on the external validity of the study (Bower *et al.*, 2005). This is a particular concern for the studies within this thesis. ME/CFS is widely recognised as a heterogeneous condition with some patients carrying out relatively normal level of physical activity whilst others may be bed bound (Jason *et al.*, 2005). This proposed study would utilise a volunteer sampling approach and it may be fair to hypothesise that the more active sub-group of people with ME/CFS may volunteer. It must also be recognised that any further impacts on the representativeness of the sample could further limit the external validity. Nevertheless, lack of representativeness does not affect the assessment of relative efficacy (treatment effect) in a definitive RCT. One method to assess the patients which are enrolled in the studies may be the use a modified version of the DePaul symptom questionnaire (Hutchinson *et al.*, 2014). This would ask patients to record the type of symptom and the severity of those symptoms which may aid in providing a description of the sample within each study.

The target sample size for the proposed pilot trial is based on adequate precision for estimating the variability in outcome to inform sample size planning for a subsequent larger trial. For a continuous outcome measure, at least 35 participants per group are required (Teare *et al.*, 2014). With an allowance for attrition (loss to follow-up) of up to 50% the target N would be 70 per group.

9.7.1 Process evaluation

The MRC (2006) guidelines stated that process evaluations can be embedded within a trial which can also be used to assess fidelity (whether the intervention was delivered as intended), dose (the quantity of intervention implemented) and reach (whether the intended audience comes into contact with the intervention, and how) (Moore *et al.*, 2015). In a definitive RCT, process evaluation may also help in clarifying causal mechanisms and identifying contextual factors associated with any variation in outcomes (MRC 2006). Whilst clinical trials provide information about the effectiveness of an intervention, Moore *et al.*, (2015) argued that effect sizes do not provide policy makers with information on how an intervention might be replicated in their specific context, or whether trial outcomes will be reproduced. Moore *et al.*, (2015) further argued that evaluation to understand how interventions work in practice is essential in developing an evidence base that informs policy and practice.

Mars *et al.* (2013) stated that intervention fidelity was under-evaluated and described intervention fidelity '*as the use of methodological strategies to monitor and enhance the reliability (i.e. the consistency) and validity (i.e. the appropriateness) of behavioural programmes.*' To try and improve fidelity Hasson (2010) states that strategies, such as provision of manuals, guidelines, training, and feedback, may be used both to optimise and to standardise implementation fidelity. Although, Mars *et al.* (2013) further stated there were two aspects that need to be assessed when measuring the fidelity, The first,

adherence is the extent to which a person delivers the essential content, delivery strategies and theories prescribed by the intervention designers. Secondly the competence refers to the level of 'skill' demonstrated by those delivering an intervention and may include the ability to respond appropriately to a wide variety of contextual cues (Mars *et al.*, 2013).

To assess this it is proposed that before the intervention begins a discussion takes place with the research team about which aspects of the design are related to behaviour change and which aspects are important to the success of the intervention. Mediating factors can also be identified and assessed as part of the fidelity assessment. This process will be underpinned by the 5 stage process developed by Walton *et al.* (2020), 1) Review fidelity checklists of other complex interventions. 2) Analyse intervention components and develop an outline. 3) Develop a fidelity checklist. 4) gain feedback from stakeholders. 5) pilot test the checklist and assess its reliability. To assess participants engagement with the intervention data from activity diaries as well as information from accelerometry will be analysed. It is proposed that a follow-up qualitative study is also conducted to gain insights into participants experiences of the intervention.

9.8 Conclusion

In conclusion the MRC framework has been used to develop a complex intervention exploring the use of a physical activity intervention in managing ME/CFS. The BCW has been applied underpinned by the intervention design

process, COM-B framework, and the TDF to identify the specific behaviour changes and techniques required for successful implementation. The intervention was developed from previous qualitative work with input from a PPI group along with discussions among the research team and underpinned from findings from three previous systematic reviews and meta-analyses. To underpin a subsequent definitive RCT of the effectiveness of the intervention a pilot RCT is proposed with a process evaluation feasibility study conducted in conjunction. The main outcomes for the RCT are physical activity levels and overall symptoms, and for the process evaluation intervention fidelity will be assessed alongside qualitative research data in people with ME/CFS. The CERT framework alongside the Michie *et al*, (2014) recommendations will be used to provide a description of the intervention.

Chapter 10: Discussion

The aim of this thesis was to explore the relationship between physical activity and ME/CFS. To achieve this aim, 3 systematic reviews with meta-analyses, as well as a qualitative study have been conducted. A patient advisory group (PAG) was developed to provide public/ patient involvement (PPI). The information from these studies and input from the PAG were synthesised to develop a physical activity intervention. The aim of this intervention was to aid in the management of symptoms and activity levels in people with ME/CFS. Unlike previous work in this field, which has focused on fatigue as a primary outcome, this intervention focuses on amount and intensity of physical activity alongside a patient-reported outcome measure (PROM) of overall symptoms.

The studies undertaken as part of this thesis have identified a number of novel findings which have contributed to the evidence base in ME/CFS. The first systematic review (chapter 5), assessed differences in peak oxygen uptake (VO_{2peak}) between those with ME/CFS and apparently healthy controls. A minimal clinically important difference (MCID) was also applied to this review. At the time of publication this was the first attempt to apply a threshold to differences in VO_{2peak} between people with ME/CFS and apparently healthy controls. Findings from this review provided evidence that those with ME/CFS may have a reduced VO_{2peak} when compared to apparently healthy controls and this may increase their risk of all-cause mortality. Although it is unclear if this is a symptom of the illness or a consequence of inactivity. It is also not clear if this reduced VO_{2peak} is universal across all people with ME/CFS or

specific to different sub-groups. If this reduced VO_{2peak} is a consequence of inactivity it is feasible that those with differing symptom types and severity may have differing effects on VO_{2peak} . However this has not been assessed in the included papers.

Peak exercise is also motivationally dependent (Edvardsen *et al.*, 2014) and there was only a limited number of studies which reported objective criteria assessing maximal effort (16 of 32). Fewer still provided this information to the reader (9 of 32). It is therefore unclear if the participants in these studies did achieve their physiological maximum, which effects the reliability of these findings as it is feasible the tests were terminated too early. Finally, these studies assessed VO_{2peak} at a single time point however very few attempted to objectively measure the consequences of high intensity exercise on this population.

To address this, 6 studies (VanNess *et al.*, 2007; Vermeulen *et al.*, 2010; Snell *et al.*, 2013; Hodges *et al.*, 2017; Nelson *et al.*, 2019; Lien *et al.*, 2019) had assessed the effects of repeat VO_{2peak} tests on physiological outcomes including; heart rate, oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and work rate (WR) (measured in Watts (W) when using a cycle ergometer) at rest, anaerobic threshold (AT) and peak exercise. As there was only a limited number of studies (6), 2 of which had been published in 2019, there had been no attempt to synthesise the evidence from these papers. Therefore a systematic review and meta

analyses were conducted (chapter 6) as part of this thesis. An MCID for change in WR at AT, was hypothesised by Nelson *et al.* (2019) of a possible range of 7.5-12.5W may be a possible discriminative threshold to identify those with ME/CFS. For the purposes of this review, based on the data provided by Nelson *et al.* (2019) and half the pooled standard deviation identified during data analysis. An MCID of 10W was estimated for the mean difference in the change (test 2 minus test 1) between people with ME/CFS and apparently healthy controls. No data was available to estimate possible MCID thresholds for the other variables.

Findings from this review provided support for the theory that there was some impairment in the ability to perform repeat high intensity exercise in two $\text{VO}_{2\text{peak}}$ tests separated by 24 hours in ME/CFS. Specifically, results demonstrated a reduced work rate at AT in the second of two maximal exercise tests in ME/CFS when compared to apparently healthy controls. The effect size was large providing evidence that WR at AT may effectively discriminate between ME/CFS and controls. This possible objective measure of ME/CFS may be able to aid in providing a diagnostic measurement of ME/CFS. These findings would add support to the argument that post-exertional malaise (PEM) may possibly be measured through the use of provocation studies (Nelson *et al.*, 2019). Although the mechanism which causes this reduction in WR is unclear, of particular note is that there was no difference reported at peak exercise. Possible mechanisms for these findings could be an impaired oxygen transport system (Vermeulen *et al.* 2010) or mitochondrial dysfunction (Tomas *et al.* 2017) or a combination of these

factors. However, presently there is no explanation for any causal factor or factors. Of note, exercise at the AT is not motivationally dependent and VO_2 and WR at AT are important measures of the capacity to participate in continuous activity (Stevens *et al.*, 2018).

This review contained 6 studies of which only 4 were used in the meta-analysis of WR and AT. Due to the very low number of studies, when considering these findings and results caution is needed. Of note, Davenport *et al.* (2020) has conducted a study assessing repeat $\text{VO}_{2\text{peak}}$ tests in people with ME/CFS. They reported a reduction in WR at AT in people with ME/CFS, yet an improvement in WR at AT in the apparently healthy control group which supports the findings of this review.

However, it should be noted that the methods used in these studies are likely to trigger or exacerbate symptoms of pain and fatigue (Snell *et al.*, 2013). These studies have undoubtedly provided essential information in understanding the condition. Two of the six studies on this topic have been published since 2019 demonstrating that this is a contemporary area of ME/CFS research. Nevertheless, the ethical considerations of purposely triggering symptoms should not be overlooked. Hodges *et al.* (2020) reported that the average recovery time for a participant with ME/CFS who undertook repeated $\text{VO}_{2\text{peak}}$ testing separated by 48 hours was 11 days. This study also reported that when the tests were conducted 72 hours apart this average recovery time reduced to 5.5 days. However when tests were conducted 24

hours apart, the recovery time was 21 days (Hodges *et al.*, 2018). Although, to assess recovery participants were asked to record how many days it took for them to feel they had recovered from the exercise testing (as they felt prior to participation). Symptoms were not recorded on each day and it is unclear what the time period for follow-up recovery time was in this studies.

It is also feasible that those who undertake these tests are a more active or a less disabled sub-group of the population. For example, it is unlikely that someone who is required to spend prolonged periods in bed would volunteer for a repeat maximal exercise test, although there is little data to support or dispute this assumption. Tests which are less physically demanding may be more applicable to a more disabled sub-group of the population which may result in more representative samples overall. Possible areas that appear to show some promise include grip strength (Nacul *et al.*, 2018). This study concluded that hand grip strength was reduced in ME/CFS, particularly in individuals with more severe illness. Nacul *et al.* (2018) argued that this may indicate muscle and fatigue-related symptoms and that hand grip strength may be a potential diagnostic tool in ME/CFS and could possibly identify ME/CFS sub-groups.

As stated in previous chapters, a physiological component of the illness would demonstrate that the current cognitive behavioural model of ME/CFS (sometimes referred to as the negative illness belief model (Vercoulen *et al.*, 1998; Clark and White, 2005; Harvey and Wessely, 2009) may not adequately

explain all sustaining processes of the illness. Advocates of the cognitive behavioural model argue that the illness is maintained through inactivity in people with ME/CFS due to a belief that excessive activity will cause a worsening of symptoms (Clark and White, 2005). This inactivity causes deconditioning which results in further fatigue and the development of ME/CFS (Clark and White, 2005). Further to this, supporters of this model argue that a belief by a person with ME/CFS of a physiological element of the illness reduces the chances of successful treatment outcomes (Moss-Morris *et al.*, 2005) and therefore treatments have involved educating people with ME/CFS that there is no physiological component of their illness (White *et al.*, 2011). Evidence from this thesis disputes this approach and provides an indication that there may indeed be an element of the condition which may inhibit their ability to participate in activity (chapter 6). This adds some weight to the argument by Davenport *et al.* (2010) that for people with ME/CFS activities and exercises should not exceed an estimated AT to mitigate the subsequent functional impairments associated with PEM. Nevertheless, future studies should explore the lowest stressor required to illicit a measurable response in ME/CFS to reduce the burden placed on the individual. This may also allow those who have significant symptoms such as those bed-bound or house-bound to participate in testing.

Findings from this thesis are that the benefits of graded exercise therapy (GET) in ME/CFS is inconclusive and there is growing evidence that GET may not be an effective management strategy for a proportion of people with ME/CFS (chapter 7). Findings in chapter 7 demonstrated that when all studies

which assessed GET in ME/CFS were included, this resulted in an improvement in fatigue which exceeded the MCID of 10%. However, when studies which used the Oxford Criteria case definition were removed this improvement reduced, demonstrating that GET did not result in a clinically significant reduction in fatigue. This may be because the Oxford Criteria case definition is relatively broad and therefore includes individuals with other fatiguing illness or who are not ill (Haney *et al.*, 2015). This would support arguments made by the IOM (2015) that the Oxford Criteria case definition should not be used in future ME/CFS studies. However, the debate over the use of exercise in ME/CFS remains unclear. Although these findings are not clinically significant, they indicate a positive effect of exercise for those with ME/CFS. This contradicts survey data indicating that GET in ME/CFS is harmful. Why this disparity exists is not clear in the current literature.

A limitation of the current work in GET and ME/CFS and chapter 7 of this thesis is the lack of a MCID used to ascertain the clinical effectiveness of these interventions. Of the studies which were included in chapter 7 there was no defined MCID. The Cochrane review by Larun *et al.* (2019) had provided a threshold in the 2019 re-analysis of the 2017 Cochrane review (Larun *et al.*, 2017). However, this was based on the 11-item Chalder Fatigue Questionnaire (0-33) only and did not take into account other measurement tools such as the Fatigue Severity Scale (FSS) or variations of the CFQ such as the 14-item (0-42) and the bimodal versions (0-11). It is of note that MCID thresholds have been defined for fatigue in other health conditions such as systemic lupus erythematosus (Goligher *et al.*, 2008), rheumatoid arthritis (Pouchot *et al.*,

2008) and multiple sclerosis (Robinson *et al.*, 2009; Rietberg *et al.*, 2010). This is a considerable limitation of the literature on this topic and defining clinically relevant threshold would aid greatly in assessing any benefit of GET. There is considerable evidence to suggest that fatigue should not be the primary outcome for these studies (Nijs *et al.*, 2004a) as participants often report a number of multisystem symptoms and not just fatigue (Nijs *et al.*, 2004a). This was supported by Murdock *et al.* (2017) who argued that PROMs targeting fatigue were not designed to measure post-exertional malaise, which is often described as a hallmark of ME/CFS. PROM which assess overall symptoms or a range of symptoms such as the DePaul Symptom Questionnaire (Jason *et al.*, 2015) may be effective PROM to assess symptoms in ME/CFS.

Nevertheless, the evidence from chapter 7 demonstrated that the direction of the effect was in favour of GET improving symptoms of fatigue in ME/CFS (although the clinical significance of this is not clear). However, this is at odds with survey data which reports a high proportion of those with ME/CFS reporting negative consequences of engaging in GET (The ME Association, 2015; Geraghty *et al.*, 2019a). Findings from the qualitative study (chapter 8) support previous work (Brown *et al.*, 2017) that people with ME/CFS appear to use benchmarks of activity as measures of 'wellness'. For example, I can now complete a 5k park run, I can go for a walk with my partner. This concept of measuring 'wellness' or recovery becomes important when considering the findings from surveys such as Geraghty *et al.* (2019a). This study reported that GET produces a negative response in 54-74% of people with ME/CFS.

However, the understanding of 'improved', 'same' and 'worse' are interpreted by those completing the survey. For example, is 'improved' the ability to walk a given distance or participate in a social activity or is this remembering symptoms at one point in time and comparing to the time of completing the survey. Is there a time period, for example, compared to this time last week, last month. How do you feel today? This lack of clarity makes it difficult to interpret these answers and infer any level of clinical significance. This is not to say that these findings should not be considered and they may make an important contribution to the evidence base, however the interpretation of 'improved' for some may mean walking further than they did the week before, for others it may be not feeling as tired. One other possible consideration is the current information about incremental activity in ME/CFS is negative and it is unclear how this influences people's perceptions of this as a treatment (Twisk and Maes, 2009; The ME Association 2015). Especially as it so closely aligned with the bio-psychosocial model of ME/CFS. Currently there is little information on this to formulate conclusions with regards to this as a possible influencing factor.

Two participants in the qualitative study (chapter 8) who had succeeded in increasing their activity levels talked of how this was linked to their mood. As findings in chapter 8 demonstrated that people with ME/CFS felt a loss of identity, it may be the case that as participants re-engage in activities they had participated in before they were unwell, this improvement in mood is linked to the sense of re-finding 'self' or their 'pre-illness identity'. Developing this concept further, a possible explanation for the variations in the effects of GET

in research findings (chapter 7) vs. patient self-reported data from surveys (ME Association 2015; Geraghty *et al.* 2019a) can be theorised. In view of the findings in chapter 6; that there is a possible physiological component of the illness. It is feasible that interventions such as GET may only be treating a component of the illness or simply one of the symptoms and may not be addressing the maintaining factors of the condition. In this instance exercise is not the variable of interest, instead a co-intervention, possibly some element of re-engaging in activity or society is the variable that has an effect. In this theory, one of the symptoms, (i.e. the psychological component of feeling a sense of loss of identity) is being managed however this has not addressed the original cause or combination of causes. As people feel re-engaged in these activities, there may be a modest improvement in mood and fatigue, however the other contributing factors (or possibly primary cause) of the illness have not been treated. It is then possible that when exercise has been prescribed more generally in practice, this was viewed by practitioners as trying to increase activity levels based on the research recommendations, rather than supporting individuals to re-engage in pre-illness activities. As exercise may not have been the activity some engaged with pre-illness, there is no connection with a sense of pre-illness identity (the variable which may have improved mood) and subsequently only modest improvements in symptoms. Alternatively, practitioners may have prioritised gradual increase in exercise intensity irrespective of how the person's symptoms were on a given day due to an underlying belief that the illness was primarily psychological and hence patients needed to exceed their perceived threshold.

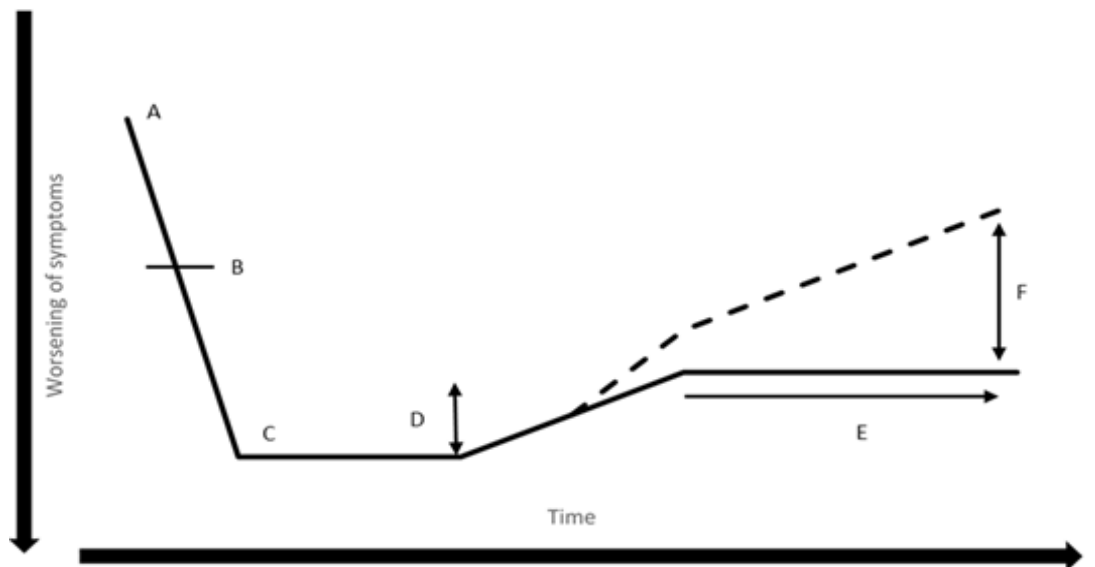
If this theory is correct, then graduated exercise programmes would not be addressing the maintaining factors, as stated by those who developed and support the cognitive behavioural model (Clark and White, 2005). Instead, based on this theory, engagement in pre-illness activity may provide some improvement in mood therefore a form of physical activity intervention could possibly support those with the illness in managing their symptoms. However this would be viewed as a long-term management strategy. Primarily, this intervention would not be underpinned by the cognitive behavioural model and instead would assume that a) there may be a physiological element of the illness which causes PEM symptoms b) any model would be a long-term management strategy and would not be aimed in 'curing' the illness and c) the aim of the programme would not be to reduce symptoms of fatigue per se, but instead to aid in engagement with activities which have meaning to the individual.

The theory of using activities which are important to the individual is not a new concept and has been discussed widely in literature which aims to improve physical activity levels in elderly (Nied and Franklin, 2002), depressive symptoms in cardiac rehabilitation (Scholz *et al.*, 2006) post-stroke (Billinger *et al.*, 2014). Nevertheless, this approach was not discussed in any of the studies reviewed in chapter 7. Often descriptions such as 'activity was negotiated' were included and it is unclear what this specifically entailed. For future work, emphasis should be placed on physical activity and not specifically exercise.

Based on the findings from chapter 8, the commonalities in the experience with those with ME/CFS were documented and depicted in figure 10.1. This model was shared with the PAG and feedback was provided from 6 members; an example of the document sent to the PAG can be found in appendix Q, pg. 370. All agreed this was a true reflection of their illness experience and there were no negative comments or criticisms of this model. One noted that in their experience, following phase D and when initially beginning phase E, they had a second relapse. It was stated that during this phase they believed they were “over the illness” and began to increase activity levels too quickly which resulted in a second decline. This feedback provides support for the need to manage activity levels, especially on days/ periods when an individual may be feeling well and is in accordance with Jason *et al.* (2005) energy envelope theory. However, it appears that for this participant, this occurred during a period when it seems those with the illness are able to increase activity levels, which is unlike Jason *et al.*’s (2005) energy envelope theory which argues that individuals should remain ‘within the envelope’ of perceived available energy. It appears that during different stages of the illness, an increase in activity levels is possible. It may be that an incremental programme may be ineffective (or less effective) during different illness stages and it maybe that programmes like the one theorised in chapter 9 may be most effective in stage D onwards. However, at present this is speculation only and there is no empirical evidence to support this hypothesis.

The model noted below is analogous with the model by Stormorken *et al.* (2017) illness trajectory model with post-infectious fatigue syndrome (figure 10.2). Although the population in Stormorken *et al.* (2017) may have some degree of cross-over with ME/CFS this is a different population. The model developed from the data in chapter 8 of this thesis also contains a number of differences. Mainly, that those interviewed (and those from the PPI group) appear to describe a minor improvement in symptoms (noted as point D in figure 10.1). This has been labelled as 'initial remission' and it appears to be a point when symptoms improve slightly followed by a period of long-term management. For those interviewed, 5 participants appeared to be in a form of 'maintenance'. During this period, participants described a good understanding of their capabilities and identified strategies to manage their illness and to increase their overall physical capabilities. Although this was still considerably lower than pre-illness levels. There were no individuals from data collected in the qualitative study and from the PPI group who reported a complete recovery (i.e. no symptoms) or had returned to pre-illness levels of activity.

Figure 10.1; Model of possible illness trajectory of ME/CFS



Key

A – Beginning of illness – unknown cause

B – Symptoms continue to worsen – may have taken steps to manage illness such as taken time from work – symptoms continue to worsen

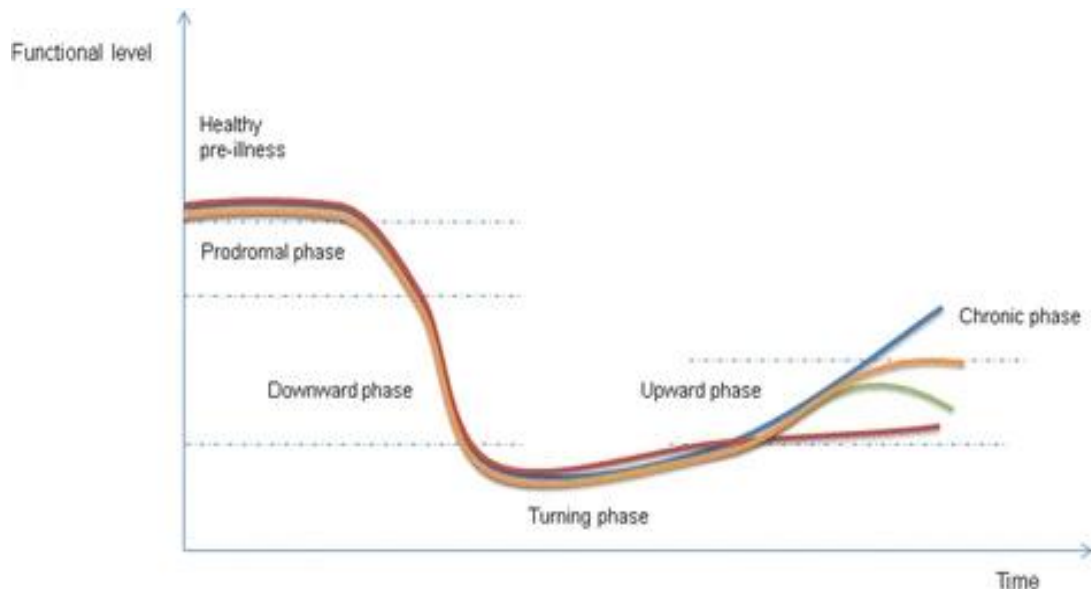
C – Symptoms reach worst point, followed by a period of severe illness

D – Initial remission – a marginal improvement in symptoms

E – Self-management – an equilibrium is found with some degree of functionality. Some achieve a minimal degree of activity; some are able to return to a relative degrees of pre-illness levels.

F – May achieve a degree of “remission” (or a new “normal”) within this range

Figure 10.2; Stormorken et al (2017), trajectory phases of people with postinfectious fatigue syndrome



An important consideration of future work in this field is establishing what is meant by recovery. Current GET studies have primarily focused on fatigue or an overall symptom score. Some studies (Moss-Morris *et al.*, 2005; Broadbent and Coutts 2016) did attempt to measure cardiovascular fitness however VO_{2peak} testing in Moss-Morris *et al.* (2005) resulted in participants refusing to partake in the post-test VO_{2peak} test (however this study also reported no adverse events). There was also no measure of total activity reported in any of the included studies. It is possible that this is because the programme was seen to be curative in design and therefore the measure of fatigue was to allow the researchers to report the proportion of participants whose fatigue had reduced. Consequently, other measures of 'success' were not measured, such as change in overall activity levels and participation in activities of daily living.

This becomes of particular importance when work such as that by Brown *et al.* (2017) and chapter 8 of this thesis provide support for the argument that in the absence of an objective diagnosis (and hence no objective measure of 'wellness'), recovery can be seen in terms of function; how far someone could walk, or their ability to participate in pre-illness activities. It is possible that by focusing on amount or type of activity, researchers and those with the illness could receive feedback on progress. Nevertheless this information is not provided in any of the included studies.

Future studies could focus on the use of provocation studies to further investigate possible physiological markers of the illness. Although, investigation of other methodologies which are less physiologically demanding on the individual may be useful in recruiting a broader range of illness severity and may provide useful information for field tests in the future. These may include studies which do not require achieving peak exercise, but other tasks such as hand grip strength or assessment of other areas such as balance. Nacul *et al.* (2018) reported that people with ME/CFS demonstrated a greater reduction in hand grip strength compared to apparently healthy controls. This may demonstrate a greater 'fatigability' in people with ME/CFS. This is of particular note when considering narratives from participants in chapter 8. For example, participants described occasions when 'they had nothing left' and their 'legs just couldn't carry' them anymore. It would be of note to assess if this perceived loss of energy is accompanied with any loss of muscle activation, which could be measured using electromyography (EMG). Alongside these studies there should be further investigation of the recovery

period and recovery 'cost' of these repeat studies to gain further insight into the consequences of these tests. The validation of outcome measures, specifically the PROM used in ME/CFS also requires further study. A further area of investigation could be areas associated with increasing activity levels in people with ME/CFS such as the intervention proposed in chapter 9.

10.1 Conclusion

The relationship between ME/CFS and physical activity appears to form a fundamental aspect of the illness experience resulting in a constant 'push and pull' between wanting to engage in everyday life while not causing a 'crash' in symptoms. The inability to engage in activities may be linked to possible feelings of loss of identity. However, an ability to re-engage with activities that have meaning to the individual may provide some short-term improvement in mood. There is a growing body of evidence of objective and measurable responses to high intensity exercise which raises questions over the existing theories associated with ME/CFS and the interventions which have been established from these. The current outcome measures used in incremental exercise interventions may not provide adequate data on both the 'active ingredient' of these interventions and their effectiveness.

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Appendix A; Abstract from Franklin *et al.* (2019)

Review	Thieme
Peak Oxygen Uptake in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Meta-Analysis	
Authors	
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Key words	
chronic fatigue syndrome, peak oxygen uptake, maximal oxygen uptake, VO ₂ peak	
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ISSN 0172-4622	
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ABSTRACT	
<p>To evaluate the magnitude of the difference in VO_{2peak} between patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME) and apparently healthy controls, 7 databases (Cochrane, PubMed, PsycINFO, Web of Knowledge, Embase, Scopus, Medline) were searched for articles published up to March 2018. Search terms included "chronic fatigue syndrome" AND ("peak" OR "maxim" OR "max") AND ("oxygen uptake" OR "oxygen consumption" OR "VO_{2peak}" OR "VO_{2max}"). Eligibility criteria were adults >18 y with clinically diagnosed CFS/ME, with VO_{2peak} measured in a maximal test and compared against an apparently healthy control group. The methodological quality of included studies was assessed using a modified Systematic Appraisal of Quality for Observational Research critical appraisal framework. A random effects meta-analysis was conducted on 32 cross-sectional studies (effects). Pooled mean VO_{2peak} was 5.2 (95% CI: 3.8–6.6) ml.kg⁻¹min⁻¹ lower in CFS/ME patients vs. healthy controls. Between-study variability (Tau) was 3.4 (1.5–4.5) ml.kg⁻¹min⁻¹ indicating substantial heterogeneity. The 95% prediction interval was –1.9 to 12.2 ml.kg⁻¹min⁻¹. The probability that the effect in a future study would be > the minimum clinically important difference of 1.1 ml.kg⁻¹min⁻¹ (in favour of controls) was 0.88 – likely to be clinically relevant. Synthesis of the available evidence indicates that CFS/ME patients have a substantially reduced VO_{2peak} compared to controls.</p>	

Appendix B; Poster from CFS/M.E. Research Collaborative Sixth Annual Science conference

People with CFS/ME demonstrate a measurable response to repeated high intensity exercise

Effects of repeat maximal exercise tests 24h apart on peak oxygen uptake and power output at the anaerobic threshold in people with CFS/ME vs healthy controls: a systematic review and meta-analysis

AIM

To quantify the size of the difference in the change in VO_{2peak} between people with CFS/ME vs apparently healthy controls in two exercise tests separated by 24h.

- Registered on Prospero register for systematic reviews: (CRD42019117837)

METHODS

Systematic review of observational studies with meta-analyses.

Overview of methods can be found by scanning QR code below.

Data Extraction

We used change data (test 2 minus test 1) for analysis.

Where change SD was not available this was estimated as described by Higgins and Green (2011):

- Convert known change SD to correlation coefficient
- Use correlation coefficient to estimate change SD in additional studies.

Data Analysis

- 6 studies (effects) included in analysis.
- DerSimonian and Laird (methods of moments) estimator with t-distribution (Knapp and Hartung) to assess heterogeneity.
- SMD calculated (pooled mean/pooled SD).
- 95% prediction interval calculated as described by IntHout et al (2016).
- MCID estimated using $\frac{1}{2}$ SD and data from Nelson et al (2019).
- Proportion of future studies estimated to produce findings that would exceed the MCID calculated using method described by Mathur and VanderWeele (2018).

RESULTS

Outcome	Pooled effect	95%CI	Tau	SMD	95%PI	MCID
VO_{2peak} (n=6)	-1.03	-3.23 to 1.17	1.29	-0.23	-5 to 3	Not defined
Peak WR (n=5)	-7.95	-15.25 to -0.64	4.29	-0.26	-21.9 to 6.03	Not defined
VO_2 AT (n=5)	-1.66	-3.67 to 0.36	1.18	-0.55	-5.51 to 2.19	Not defined
WR AT (n=4)	-20.64	-40.95 to -0.33	11.46	-0.95	-62.39 to 21.11	10W

SMD – standardised mean difference (Cohen's d). VO_{2peak} (ml.kg⁻¹.min⁻¹). Peak WR – peak work rate (W). VO_2 AT – VO_2 at anaerobic threshold (ml.kg⁻¹.min⁻¹). WR AT – work rate at anaerobic threshold (W). 95%PI – 95% prediction interval. MCID – minimal clinically important difference.

DISCUSSION

- We estimate 82% (95%CI 44% to 100%) of future studies assessing WR at AT between people with CFS/ME and controls will demonstrate a difference greater than the MCID of 10W - in favour of controls.
- Large effect size indicating the WR at AT effectively discriminates between CFS/ME and controls.
- Findings add weight to the theory of an inability of those with CFS/ME to maintain aerobic respiration at the same exercise intensity in the 24h following high intensity exercise.

Key points

- Evidence indicates a measurable, physiological difference in people with CFS/ME vs. apparently healthy controls.
- Findings support the hypothesis of a physiological component of the illness.
- May be useful to aid with an objective diagnostic test in future studies.

Authors: John Franklin,
Professor Greg Atkinson,
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Appendix C; Poster from Teesside University Postgraduate Conference

Peak Oxygen Uptake is Reduced in Patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis?

John Franklin, PhD student

<p>Aim</p> <p>To explore the magnitude of the difference in VO_{2peak} in CFS/ME patients compared to apparently healthy controls.</p> <p>Background</p> <p>CFS/ME Chronic fatigue syndrome/ myalgic encephalomyelitis (CFS/ME) is a debilitating disease with symptoms including severe fatigue, cognitive dysfunction and post exertional malaise. Believed to effect between 0.2-0.4% of the population (NICE 2007).</p> <p>It has been demonstrated that CFS/ME patients are less physically active than controls (Evering et al 2011).</p> <p>Peak Oxygen Uptake (VO_{2peak})</p> <p>VO_{2peak} is a measure of cardiorespiratory fitness and sets the upper limit for relatively sustainable energy expenditure.</p> <p>Laukkanen et al reported that a $1\text{ml.kg}^{-1}\text{min}^{-1}$ increase in VO_{2peak} reduced all cause mortality by 9% in healthy adults.</p> <p>Reduced physical activity is associated with a reduced VO_{2peak}. As CFS/ME patients are less active it is important to assess if this is associated with a decrease in VO_{2peak}.</p> <p><small>Contributors Professor Alan Batterham (DoS), Professor Greg Atkinson, Jan Atkinson</small></p>	<p>Methods</p> <ul style="list-style-type: none"> • Systematic review with meta-analysis • 7 databases search • 32 observational studies included • Quality assessed using the SAQOR • Conducted a random effects meta-analysis (DerSimonian and Laird with z-distribution) • Eggers regression used to assess small study effects • MCID calculated using anchor based approach based on Laukkanen et al 2016. • HR 0.9 – MCID ('small') – $1.1\text{ ml.kg}^{-1}\text{min}^{-1}$ • HR 0.7 – 'moderate' effect $3.8\text{ ml.kg}^{-1}\text{min}^{-1}$ • HR 0.5 – 'large' effect $7.3\text{ ml.kg}^{-1}\text{min}^{-1}$ 	<p>Results</p> <p>Pooled mean VO_{2peak} was $5.2\text{ml.kg}^{-1}\text{min}^{-1}$ lower in CFS/ME patients vs apparently healthy controls (95%CI 3.8 to 6.6). Tau, the between study variability was 3.4 (95%CI 1.5 to 4.5) $\text{ml.kg}^{-1}\text{min}^{-1}$ indicating substantial heterogeneity.</p> <p>The 95% prediction interval (PI) – indicating the probability that a future study would find exceed the MCID was 95%PI -1.9 to 12.2.</p> <p>Study quality accounted for 11% of between study variance.</p> <p>The probability that a future study would exceed the MCID is 88%.</p> <p>The probability that a future study would exceed the moderate effect of $3.8\text{ ml.kg}^{-1}\text{min}^{-1}$ is 65%.</p> <p>Conclusion</p> <p>CFS/ME patients have a substantially reduced VO_{2peak} which may increase their risk of cardiovascular and all-cause mortality.</p> <p><small>References Evering, R.M.H., Van Weering, M.G.H., Groothuis-Oudshoorn, K.C.G.M. (2011) Daily physical activity of patients with the chronic fatigue syndrome: a systematic review. <i>Clinical Rehabilitation</i>. 25 pp112-133. Laukkanen, J.A., Zaccardi, F., Khan, H., Kurl, S., Jaki, S.V. and Rauramaa, R. (2016) Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study. <i>Mayo Clin Proc</i>. 91(9) pp1183-1188.</small></p>
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Fig. 1 Flow diagram of study selection

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graph TD
    subgraph Identification
        A[Records identified through database searching  
(n = 436)]
        B[Additional records identified through other sources  
(n = 3)]
    end
    A --> C[Records after duplicates removed  
(n = 441)]
    B --> C
    subgraph Screening
        C --> D[Records screened  
(n = 441)]
        D --> E[Records excluded  
(n = 379)]
    end
    subgraph Eligibility
        D --> F[Full-text articles assessed for eligibility  
(n = 62)]
        F --> G[Full-text articles excluded, with reasons  
(n = 30)]
    end
    subgraph Included
        F --> H[Studies included in quantitative synthesis (meta-analysis)  
(n = 32)]
    end
    
```

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Appendix D; Calculations for correlation coefficients and change standard deviations (Chapter 6)

Exploring the Relationship between Physical Activity and ME/CFS

Data available from papers or authors:

Study	Sample Size CFS	Sample size control	Total sample size	Mean change CFS	SD of change CFS	Mean change control	SD of change control
Vermeulen et al (2010)	15	15	30	-1.33	1.68	0.73	1.39
Hodges et al (2017)	10	10	20	1.32	3.04	1.08	1.25

Table 1

Data available from papers but no other information provided after contacting authors:

Study	Sample size CFS	Sample size control	Total sample size	CFS T1 mean and SD	CFS T2 mean and SD	Control T1 mean and SD	Control T2 mean and SD
VanNess et al (2007)	6	6	12	26.23 (4.92)	20.47 (1.80)	28.43 (7.27)	28.90 (8.06)
Snell et al (2013)	51	10	61	21.51 (4.09)	20.44 (4.47)	25.04 (4.41)	23.96 (4.30)

Table 2

I've used the data from Vermeulen et al (2010) to calculate the correlation coefficients, my thinking was

1. Although marginal the sample size was slightly larger
2. The direction of the change in the Vermeulen was the same for the CFS/ME group as both of the papers in table 2

The Cochrane guidance stated that you need to be aware of the following points:

1. Was the same scale used - yes
2. Same degree of measurement error – a fair assumption
3. Same time period between test 1 and test 2 (states pre and post) – yes

The correlation coefficient for the Hodges paper as well as the Cochrane handbook stated that 'before imputation is undertaken it is recommended that correlation coefficients are computed for many (if not all) studies in the meta-analysis and it is noted whether or not

Exploring the Relationship between Physical Activity and ME/CFS

they are consistent. Imputation should be done only as a very tentative analysis if correlations are inconsistent.'

Calculations taken from Cochrane section 16.1.3.2

	Test 1 mean (SD)	Test 2 mean (SD)	Change mean (SD)
CFS/ME group	22.3 (5.7)	20.9 (5.5)	-1.33 (1.68)
Sample size: 15	Mean(1) SD(1)	Mean(2) SD(2)	Mean(3) SD(3)
Control group	31.2 (7.0)	31.9 (7.4)	0.73 (1.39)
Sample size: 15	Mean(4) SD(4)	Mean(5) SD(5)	Mean(6) SD(6)

Table 3; data take from Vermeulen et al (2010)

$$\text{Corr}^{\text{CFS}} = (\text{SD}(1)^2 + \text{SD}(2)^2 - \text{SD}(3)^2) / (2 * \text{SD}(1) * \text{SD}(2))$$

$$\text{Corr}^{\text{CFS}} = (5.7^2 + 5.5^2 - 1.68^2) / (2 * 5.7 * 5.5)$$

$$\text{Corr}^{\text{CFS}} = (32.49 + 30.25 - 2.8224) / 62.7$$

$$\text{Corr}^{\text{CFS}} = 59.9176 / 62.7 = \mathbf{0.96}$$

$$\text{Corr}^{\text{con}} = (\text{SD}(4)^2 + \text{SD}(5)^2 - \text{SD}(6)^2) / (2 * \text{SD}(4) * \text{SD}(5))$$

$$\text{Corr}^{\text{con}} = (7.0^2 + 7.4^2 - 1.39^2) / (2 * 7 * 7.4)$$

$$\text{Corr}^{\text{con}} = (49 + 54.76 - 1.9321) / 103.6$$

$$\text{Corr}^{\text{con}} = 101.8279 / 103.6 = \mathbf{0.98}$$

	Test 1 mean (SD)	Test 2 mean (SD)	Change mean (SD)
CFS/ME group	24.95 (8.9)	26.27 (7.78)	1.32 (3.04)

Exploring the Relationship between Physical Activity and ME/CFS

Sample size: 10	Mean(1) SD(1)	Mean(2) SD(2)	Mean(3) SD(3)
Control group	31.99 (10.88)	33.06 (12.5)	1.08 (1.25)
Sample size: 10	Mean(4) SD(4)	Mean(5) SD(5)	Mean(6) SD(6)

Table 4; data take from Hodges et al (2017)

$$\text{Corr}^{\text{CFS}} = (\text{SD}(1)^2 + \text{SD}(2)^2 - \text{SD}(3)^2) / (2 * \text{SD}(1) * \text{SD}(2))$$

$$\text{Corr}^{\text{CFS}} = (8.9^2 + 7.78^2 - 3.04^2) / (2 * 8.9 * 7.78)$$

$$\text{Corr}^{\text{CFS}} = (79.21 + 60.5284 - 9.2416) / 138.484$$

$$\text{Corr}^{\text{CFS}} = 130.4968 / 138.484 = \underline{\mathbf{0.94}}$$

$$\text{Corr}^{\text{con}} = (\text{SD}(4)^2 + \text{SD}(5)^2 - \text{SD}(6)^2) / (2 * \text{SD}(4) * \text{SD}(5))$$

$$\text{Corr}^{\text{con}} = (10.88^2 + 12.5^2 - 1.25^2) / (2 * 10.88 * 12.5)$$

$$\text{Corr}^{\text{con}} = (118.3744 + 156.25 - 1.5625) / 272$$

$$\text{Corr}^{\text{con}} = 273.0619 / 272 = \underline{\mathbf{1.00}}$$

Data used from Vermeulen et al (2010) (The first set of equations on page 2 CFS/ME group 0.96 and the control group 0.98.

Calculating the SD of the change

Exploring the Relationship between Physical Activity and ME/CFS

VanNess et al (2007)

	Test 1 mean (SD)	Test 2 mean (SD)	Change mean (SD)
CFS/ME group	26.23 (4.92)	20.47 (1.80)	-5.76 (not known)
Sample size: 6	Mean(1) SD(1)	Mean(2) SD(2)	Mean(3) SD(3)
Control group	28.43 (7.27)	28.90 (8.06)	0.47 (not known)
Sample size: 6	Mean(4) SD(4)	Mean(5) SD(5)	Mean(6) SD(6)

Tab 5; Data taken from VanNess et al (2007)

$$\text{CFS/ME} - \text{Corr}^{\text{CFS}} = 0.96$$

$$\text{Control} - \text{Corr}^{\text{con}} = 0.98$$

CFS/ME group

$$\text{SD}^{\text{change}} = \sqrt{\text{SD}(1)^2 + \text{SD}(2)^2 - (2 * \text{Corr}^{\text{CFS}} * \text{SD}(1) * \text{SD}(2))}$$

$$= \sqrt{4.92^2 + 1.80^2 - (2 * 0.96 * 4.92 * 1.8)}$$

$$= \sqrt{24.2064 + 3.24 - (17.00352)}$$

$$= \sqrt{27.4464 - 17.00352}$$

$$= \sqrt{10.44288} = \mathbf{3.23}$$

Control group

$$\text{SD}^{\text{change}} = \sqrt{\text{SD}(4)^2 + \text{SD}(5)^2 - (2 * \text{Corr}^{\text{CFS}} * \text{SD}(4) * \text{SD}(5))}$$

$$= \sqrt{7.27^2 + 8.06^2 - (2 * 0.98 * 7.27 * 8.06)}$$

$$= \sqrt{52.8529 + 64.9636 - 114.848552}$$

Exploring the Relationship between Physical Activity and ME/CFS

$$= \sqrt{117.8165 - 114.848552}$$

$$= \sqrt{2.967948} = \underline{\underline{1.72}}$$

Snell et al (2013)

	Test 1 mean (SD)	Test 2 mean (SD)	Change mean (SD)
CFS/ME group	51.51 (4.09)	20.44 (4.47)	-1.07 (not known)
Sample size: 51	Mean(1) SD(1)	Mean(2) SD(2)	Mean(3) SD(3)
Control group	25.04 (4.41)	23.96 (4.30)	-1.08 (not known)
Sample size: 10	Mean(4) SD(4)	Mean(5) SD(5)	Mean(6) SD(6)

Table 6; Data taken from Snell et al (2013)

$$\text{CFS/ME} - \text{Corr}^{\text{CFS}} = 0.96$$

$$\text{Control} - \text{Corr}^{\text{con}} = 0.98$$

CFS/ME group

$$\text{SD}^{\text{change}} = \sqrt{\text{SD}(1)^2 + \text{SD}(2)^2 - (2 * \text{Corr}^{\text{CFS}} * \text{SD}(1) * \text{SD}(2))}$$

$$= \sqrt{4.09^2 + 4.47^2 - (2 * 0.96 * 4.09 * 4.47)}$$

$$= \sqrt{16.7281 + 19.9809 - 35.102016}$$

$$= \sqrt{36.709 - 35.102016}$$

$$= \sqrt{1.606984} = \underline{\underline{1.27}}$$

Control group

$$\text{SD}^{\text{change}} = \sqrt{\text{SD}(4)^2 + \text{SD}(5)^2 - (2 * \text{Corr}^{\text{CFS}} * \text{SD}(4) * \text{SD}(5))}$$

$$= \sqrt{4.41^2 + 4.3^2 - (2 * 0.98 * 4.41 * 4.3)}$$

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$$= \sqrt{19.4481 + 18.49 - 37.16748}$$

$$= \sqrt{37.9381 - 37.16748}$$

$$= \sqrt{0.77062} = \underline{\underline{\mathbf{0.88}}}$$

Exploring the Relationship between Physical Activity and ME/CFS

Appendix E; Assessment of methodological quality for Chapter 6

Table xx; Overview of assessment of methodological quality							
	Question on framework	Vermeulen et al (2010)	Hodges et al (2017)	VanNess et al (2007)	Snell et al (2013)	Nelson et al (2019)	Lien et al (2019)
CFS/ME group	Q1. The source of the sample is clearly stated	Good <i>'Patients who attended the CFS/ME clinic Amsterdam'</i>	Not reported	Adequate <i>'CFS patients were referred for exercise testing following pre-screening by their primary care physician'</i>	Adequate <i>'The women were either recruited specifically as research participants or referred by a treating physician for functional assessment.'</i>	Good <i>'ME/CFS were recruited via specialist clinics in ME/CFS support groups from the Adelaide, South Australia Greater Metropolitan area.'</i>	Adequate <i>'We used social network and media coverage to invite potential participants'</i>
	Q2. The sampling method is described (e.g. consecutive, clinical, community, convenience)	Not reported	Not reported	Not reported	Adequate <i>'A sample of convenience...'</i>	Not reported	Not reported
	Q3. The sample size	Not reported	Not reported	Not reported	Not reported	Not reported	Good

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	is appropriate to determine statistical significance for primary outcomes					‘To demonstrate a difference of 10% between the two tests, corresponding to 2.23 mL/kg/min, with a two-sided significance level of 5% and 80% power; our study would require a sample size of 18 participants in the ME/CSF group.’	
Q4. Entry criteria and exclusions are stated and justified	Good	Good	Good	Good	Good	Good	Good
	<i>‘All patients fulfilled the criteria of Fukuda et al for CFS/ME and reported the start of symptoms after an infectious disease. Exclusion criteria were according to Fukuda et al [1]. Contra</i>	<i>‘CFS/ME participants were included if they met all three case definitions: Fukuda case definition, the Canadian Consensus Criteria and the International Consensus Criteria... Exclusion criteria included symptomatic heart failure,</i>	<i>‘... diagnosis of CFS according to the criteria established by Fukuda et al... Individuals with concurrent medical disorders, or who had been treated with drugs that modulate the immune, cardiovascular, or respiratory system within six weeks of testing were excluded...</i>	<i>‘All participants with CFS met the criteria established by Fukuda et al for the diagnosis of CFS. In addition, all participants with CFS reported exacerbation of physical activity as a specific aspect of their diagnoses.’</i>	<i>‘All participants were required to be between the ages of 18–65 years, and ME/CFS patients had to have been previously diagnosed with ME/CFS based on one of three widely accepted</i>	<i>‘All requests were pre-screened with regard to age (18–50 years), gender (females), place of living (in the study area), health status, medication, and current level of physical activity. Eligible candidates were interviewed consecutively on</i>	

	<p>indications for the CPET were mainly cardiac diseases, hypertension, or the inability to perform the exercise as in arthrosis of the knee.</p> <p>Medication was discontinued 2 weeks before the first test'</p>	<p>unstable angina, symptomatic peripheral arterial disease, dementia disorders which or aphasia and other medical conditions that prohibit aerobic exercise'.</p>	<p>disqualified from the study patients with medical disorders which may have interfered with their ability to perform the graded exercise test.'</p>	<p>diagnostic criteria: 1994 Centers For Disease Control and Prevention (CDC 1994—also known as the 'Fukuda' criteria, 2003 'Canadian' Consensus Criteria (CCC), or 2011 International Consensus Criteria (ICC)... All participants were required to be sedentary (< 150 min of moderate physical activity per week) and were excluded if they were taking any medication or had any known medical</p>	<p>telephone or in person. All included patients fulfilled the CCC for ME/CFS (Carruthers et al. 2003). We excluded patients who were pregnant, bedridden or had comorbidities that could interfere with CPET results, that is, lung- and heart disorders, or used medication known to affect physical performance.'</p>
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Exploring the Relationship between Physical Activity and ME/CFS

						<i>conditions (excluding ME/CFS) which could alter the response to exercise (e.g. beta-blockers, anti-depressants/postural orthostatic tachycardia syndrome).'</i>	
Control/ comparison group	Q5. Control group is included	Good Control group included	Good Control group included	Good Control group included	Good Control group included	Good Control group included	Good Control group included
	Q6. The control group is easily identifiable	Good	Good	Good	Good	Good	Good
	Q7. The source of the controls is explained and is appropriate	Not reported	Not reported	Not reported	Not reported	Good <i>'...healthy participants were recruited to act as controls using convenience sampling from patient and research</i>	Adequate <i>'We used social network and media coverage to invite potential participants'</i>

Exploring the Relationship between Physical Activity and ME/CFS

					centre networks.'	
Q8. Controls are matched or randomised	Not reported	Good <i>'Gender and age- matched controls' only</i>	Good <i>Included women only</i>	Good <i>'Efforts were made to match participants with CFS with control participants for age and body mass index.'</i>	Good <i>'Controls were matched to ME/CFS patients on the basis of age, body mass index (BMI) and physical activity status.'</i>	Not reported
Q9. Statistical differences between cases and controls have been controlled for	Good Reported in table 1	Not reported	Not reported	Good <i>'No significant differences were found between participants with CFS and control participants for age, height, weight, or body mass index (P>.05).'</i> Reported in table 1	Good Reported in table 1	Good Reported in table 1. Weight and BMI showed significant differences with larger weight and BMI in the CFS/ME group
Q10. Adequate	Good	Good	Good	Good	Good	Good

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Quality of exposure/outcome measurements	assessment of exposure	<i>'All patients fulfilled the criteria of Fukuda et al for CFS/ ME'</i>	<i>'CFS/ME participants were included if they met all three case definitions: Fukuda case definition, the Canadian Consensus Criteria and the International Consensus Criteria'.</i>	<i>'Individuals with a confirmed and rigorous diagnosis of CFS according to the criteria established by Fukuda et al...'</i>	<i>'All participants with CFS met the criteria established by Fukuda et al.'</i>	<i>'ME/CFS patients had to have been previously diagnosed with ME/CFS based on one of three widely accepted diagnostic criteria: 1994 Centers For Disease Control and Prevention (CDC 1994—also known as the 'Fukuda' criteria, 2003 'Canadian' Consensus Criteria (CCC), or 2011 International Consensus Criteria (ICC)'</i>	<i>'All included patients fulfilled the CCC for ME/CFS (Carruthers et al. 2003)'</i>
	Q11. Adequate measure of outcome(s)	Adequate <i>'V'E, V'O₂, and V'CO₂ and oxygen</i>	Good <i>'Online respiratory measurements including oxygen</i>	Poor <i>'Oxygen consumption was</i>	Good <i>'Breath-by-breath gas samples were collected with a</i>	Good <i>'...were connected to an</i>	Good <i>'Gas exchange and ventilation were measured</i>

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		<i>saturation were continuously measured (metasoft)'</i>	<i>consumption (ml.kg-1min-1), carbon dioxide production (l.min-1) and respiratory exchange ratio were measured using a two-way breathing valve and were recorded in 10s intervals. The online breath-by-breath system (Turbofit)...</i>	<i>measured breath by breath'</i>	<i>comfortably fitted Hans Rudolph face mask (Hans Rudolph Inc, Shawnee, Kansas) and analysed throughout the test with a Jaeger Oxycon Alpha metabolic cart (CareFusion Corp).'</i>	<i>indirect calorimetry system (TrueOne 240 0, Parvo Medics, East Sandy, Utah) via a two-way non-rebreathing value (Hans-Rudolph inc., Shawnee, Kansas).'</i>	<i>breath-by- breath (Oxycon Pro). The flow sensor was calibrated with a 3 L syringe prior to each test (Hans Rudolph, Shawnee, KS), and the gas analyser for O2 and CO2 was calibrated against commercial standards.'</i>
	Q12.	Adequate	Good	Adequate	Good	Good	Adequate
Distorting influences	Exercise test described adequately	<i>'3 min without activity, 3 min of unloaded pedalling, followed by pedalling against increasing resistance until exhaustion'</i>	<i>Participants cycled on an electromagnetically braked cycle ergometer (Lode...) at between 50 and 80 rpm. Cycle seat was positioned at approximately 175 of knee extension, and same height was used on both occasions. Starting at 15W,</i>	<i>'The CFS patients performed a modified Bruce treadmill protocol (n = 2) or a 10W/min ramping protocol on a cycle ergometer (n = 4). The control subjects performed 20W/min ramping protocol (n = 6).'</i>	<i>'The protocol included 3 minutes of rest followed by 1 minute of unloaded cycling before the exercise test. Participants were asked to maintain a pedalling cadence of 60 to 80 rpm throughout the test. For the test, workload was increased progressively at a rate of 5 W/20 s (15 W/min)'</i>	<i>'Participants were then seated on the bicycle ergometer, fitted with the valve for the indirect calorimetry system, and told to rest quietly while sitting on the bike. Following a 2-min resting phase and 2 min</i>	<i>'The rate was based on previous and current level of activity, physical examination, age, height and weight, and ranged from 10 to 24 W/min for the ME/CFS patients, and 15–30 W/min for the controls. The protocol included</i>

Exploring the Relationship between Physical Activity and ME/CFS

		<p><i>the intensity was increased at a rate of 15W/min'</i></p>			<p><i>period of 4–6 min, participants were instructed to commence cycling at a self-selected cadence for 5 min at 40 W for males and 30 W for females, which served as a warm-up. Following the initial 5 min of steady state exercise, the work rate was increased by 5 W increments every 20 s, until volitional exhaustion. All participants were given frequent verbal encouragement throughout.'</i></p>	
Q13. Criteria used to assess	Not reported	Adequate	Poor	Adequate	Adequate	Not reported
		'The test was terminated	Stated in discussion: '...all	'All participants achieved a	'peak $\dot{V}O_2$ is typically done	

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maximum effort	voluntarily by the participant or when they were unable to maintain a pedal frequency of 50W or the ACSM termination criteria were met.'	<i>patients in the present study met criteria for maximum effort on both tests.'</i>	<i>respiratory exchange ratio (RER) of greater than or equal to 1.1...In addition to an RER of greater than or equal to 1.1, all participants met at least 1 other criterion for determining peak effort (i.e., a plateau in oxygen consumption, a rating of perceived exertion of >17, or a (1) heart rate of >85% of the age-predicted maximum).'</i>	<i>by identifying a plateau in $\dot{V}O_2$'</i>
		Details of criteria not provided.	<i>1.1...In addition to an RER of greater than or equal to 1.1, all participants met at least 1 other criterion for determining peak effort (i.e., a plateau in oxygen consumption, a rating of perceived exertion of >17, or a (1) heart rate of >85% of the age-predicted maximum).'</i>	<i>'values were considered to have reached a valid maximal level if participants fulfilled two or more secondary criteria: achievement of at least 90% of age predicted maximal HR, (2) respiratory exchange ratio (RER) > 1.1, and RPE \geq 17'</i>
			Data demonstrating how many fulfilled each criteria for max not provided.	<i>'All participants met at least two of the three criteria required for determination of a valid</i>

						<i>maximal effort during exercise testing.'</i>
						Data demonstrating how many fulfilled each criteria for max not provided.
Q14.	Not reported	Good	Good	Not reported	Good	Adequate
Attempts made to control for other extraneous variables.		<i>'Participants were instructed to avoid food or smoking <2h, caffeine <4h and strenuous exercise 24 h prior...'</i>	<i>'Subjects were instructed to avoid food, alcohol and caffeine for at least three hours prior to testing. ...asked to avoid significant exertion or exercise for 24 hours prior to testing.'</i>		<i>'Participants first attended the laboratory for an initial habituation session, during which they were familiarised with the laboratory and with the questionnaires and procedures to be used during the study.'</i>	<i>'All tests were performed between 8 and 11 AM... The participants were asked to refrain from physical exertion 72 h prior to the first CPET and were tested after an overnight fasting, allowing free consumption of water.'</i>
		<i>'Cycle seat was positioned at approximately 175 of knee extension, and same height was used on both occasions.'</i>				
		<i>'The laboratory environment remained 17-18 degree Celsius...'</i>				

Exploring the Relationship between Physical Activity and ME/CFS

Reporting of data	Q15. Explanation of missing data given	Not reported	Not reported	Not reported	Not reported	Not reported	Adequate
							Data reported in figure 1 but no explanation provided
	Q16. Data are clearly and accurately presented including CI where appropriate	Adequate	Adequate	Adequate	Adequate	Adequate	Poor
		Data reported as means and SDs including mean change and SD of change.	Data reported as means and SDs. Mean change and SD of the change is not reported.	Data reported as means and SDs. Mean change and SD of the change is not reported.	Data reported as means and SDs. Mean change and SD of the change is not reported.	Data reported as means and SDs. Mean change and SD of the change is not reported.	Data reported as means and SDs. Mean change and SD of the change is not reported.
		P-values used to report statistical significance	P-values used to report statistical significance	P-values used to report statistical significance	P-values and 95% CI used to report statistical significance	P-values used to report statistical significance	Data reported in figures which requires software to digitise.
		Possible error table 3. Change SD for control group for max HR 41.6 beats/min.					Possible error in figure 5.D. – resulting in this data being excluded from the review
	Total score	15	18	13	20	24	19

Scoring: 'Not reported/ Poor' resulted in a score of 0, 'Adequate' resulted in a score of 1, 'Good' resulted in a score of 2. Maximum score 32.

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Appendix F; Teesside University School of Health and Social Care Ethical Approval (Chapter 8)

Teesside University
Middlesbrough Tees Valley
TS1 3BA UK
www.tees.ac.uk



PRIVATE AND CONFIDENTIAL

Direct Line: 01642 384124

5th September 2017

Alan Batterham

School of Health & Social Care

Teesside University

Dear Alan

Study No 225/16 - A phenomenological study of patients with Chronic Fatigue Syndromes (CFS) experiences of physical activity. Researcher: John Franklin.
Supervisor: Alan Batterham.

Decision: Approved

Thank you for submitting an amended application pack. I am pleased to confirm that the comments raised by the School of Health & Social Care Research Governance and Ethics Committee have been addressed in your amended application pack and your study has been approved through Chair's Action. Your study may proceed as it was described in your approved application pack. The application was presented on an IRAS generated NHS REC form.

Please note:

If another body was not named as the Sponsor, in the application documents reviewed, Teesside University, acting through its School of Health & Social Care, will act as Sponsor for the project.

John Franklin

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Where applicable, your study may only commence after you have also received written approval/permission from any external stakeholders (e.g. HRA Approval, National Institutes of Health Approval for Conducting Research in the Ministry of Health Malaysia and/or Malaysian Ministry of Health Ethical and Medical Research

Committee etc.) and/or any operational / management structures relevant (e.g. Heads of Dept., Service Managers etc.). A copy of this letter **must** be included in any applications to any external stakeholders. Copies of all approvals/permissions granted, by any external stakeholders, must be forwarded to the RG&EC Secretary (for inclusion in TU's record of the project) as soon as possible after you receive them.

If you wish to make **any** changes to the project methods and/or supporting documentation, (other than those required as urgent safety measures) you must obtain Ethical Clearance for those, from TU, (by application to the School RG&EC), **before** you may implement any changes, and (if applicable), **before** you apply for approval/permission from any external stakeholders. Should you make any changes, without prior permission, as urgent safety measures; as soon as possible after the event you must provide details of those, in writing, to myself and all other relevant bodies. All substantive work on the project must be suspended and cannot restart until written approval for those changes has been obtained from the RG&EC and all other relevant external stakeholders. Please note: for certain DH classifications of study, the HRA (and other stakeholders) stipulate set time limits for such reporting, which you must adhere to.

VAT REG NO. GB 686 4809 81

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Middlesbrough Tees Valley
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INVESTOR IN PEOPLE



On behalf of the School of Health & Social Care Research Governance and Ethics Committee please accept my best wishes for success in completing your study.

John Franklin

Investigating the Relationship Between Physical Activity/ Exercise and
CFS/ME

Yours sincerely



Dr. Alasdair MacSween

Chair Research Governance and Ethics Committee School of Health & Social Care

VAT REG NO. GB 686 4809 81



INVESTOR IN PEOPLE

WoSRES
West of Scotland Research Ethics Service

Professor Alan Batterham
C1.19 Constantine Building
Research Institute
School of Health and Social Care, Teesside University,
TS1 3BA



West of Scotland REC 3
Research Ethics
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ
(Formerly Yorkhill Childrens Hospital)

Date 20 October 2017
Direct line 0141 232 1807
E-mail WoSREC3@ggc.scot.nhs.uk

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

Dear Professor Batterham

Study title: A phenomenological study of experiences of physical activity in patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis.
REC reference: 17/WS/0197
IRAS project ID: 212399

Thank you for your letter of 17 October 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rtforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Confirmation of any other Regulatory Approvals (e.g. CAG) and all correspondence [University Ethical Approval]	1	02 May 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance]	1	15 July 2017
GP/consultant information sheets or letters [GP letter template]	1	13 October 2017
Interview schedules or topic guides for participants [Interview Schedule]	1	21 June 2017
IRAS Application Form [IRAS_Form_06092017]		06 September 2017
Letters of invitation to participant [Study Introduction]	1	21 June 2017
Other [Patient Advisory Group Advert]	1	21 June 2017
Other [Further ethical approval following advisory comments]	1	06 September 2017
Participant consent form [Consent form]	3	17 October 2017
Participant information sheet (PIS) [PIS]	3	17 October 2017
Research protocol or project proposal [Research Protocol]	2	13 October 2017
Response to Request for Further Information [Response letter]		17 October 2017
Summary CV for Chief Investigator (CI) [A.Batterham CV]	1	21 June 2017
Summary CV for student [Student CV]	1	21 June 2017
Summary CV for supervisor (student research) [G.Atkinson CV]	1	21 June 2017
Summary CV for supervisor (student research) [S.Harrison CV]	1	21 June 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

17/WS/0197

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Abibat Adewumi

On behalf of
Dr Adam Burnel
Chair

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Mrs Marion Grieves
Julie Rowbotham, South Tees Hospital NHS Trust*



Health Research Authority

Professor Alan Batterham
C1.19 Constantine Building
Research Institute
School of Health and Social Care, Teesside University
TS1 3BA

Email: hra.approval@nhs.net

26 October 2017

Dear Professor Batterham

Letter of HRA Approval

Study title:	A phenomenological study of experiences of physical activity in patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis.
IRAS project ID:	212399
REC reference:	17/WS/0197
Sponsor	Teesside University

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read *Appendix B* carefully, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *“After Ethical Review – guidance for sponsors and investigators”*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](http://www.hra.nhs.uk), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](http://www.hra.nhs.uk).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

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procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

Your IRAS project ID is 212399. Please quote this on all correspondence.

Yours sincerely

Simon Connolly
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Marion Grieves, Teesside University*



IRAS project ID	212399
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Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance]	1	15 July 2017
GP/consultant information sheets or letters GP letter template]	1	13 October 2017
HRA Schedule of Events	1	
HRA Statement of Activities	1	
Interview schedules or topic guides for participants [Interview Schedule]	1	21 June 2017
IRAS Application Form [IRAS_Form_06092017]		06 September 2017
Letters of invitation to participant [Study Introduction]	1	21 June 2017
Other [Patient Advisory Group Advert]	1	21 June 2017
Participant consent form [Consent form]	3	17 October 2017
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Summary CV for student [Student CV]	1	21 June 2017
Summary CV for supervisor (student research) [G.Atkinson CV]	1	21 June 2017
Summary CV for supervisor (student research) [S.Harrison CV]	1	21 June 2017

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Marion Grieves
Tel: 01642 384962
Email: m.grieves@tees.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	Statement of activities and schedule of events provided. Although formal confirmation of capacity and capability is not expected of all or some organisations participating in this study (see <i>Confirmation of Capacity and Capability</i> section for full details), and such organisations would therefore be assumed to have confirmed their capacity and capability should they not

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

IRAS project ID	212399
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Section	HRA Assessment Criteria	Compliant with Standards	Comments
			respond to the contrary, we would ask that these organisations pro-actively engage with the sponsor in order to confirm at as early a date as possible. Confirmation in such cases should be by email to the CI and Sponsor.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	Study completed towards doctorate.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

This is a Teesside University study completed by a doctoral student. The involvement of the NHS organisation is limited to providing information about the study to potential participants.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

The HRA has determined that participating NHS organisations in England are **not expected to formally confirm their capacity and capability to host this research**, because their involvement is limited to providing information about a university study to potential participants.

- The HRA has informed the relevant research management offices that you intend to undertake the research at their organisation. However, you should still support and liaise with these organisations as necessary.
- Following issue of the HRA Approval letter, and subject to the two conditions below, it is expected that these organisations will become participating NHS organisations 35 days after issue of this Letter of HRA Approval (no later than 30 November):
 - You may not include the NHS organisation if they provide justification to the sponsor and the HRA as to why the organisation cannot participate
 - You may not include the NHS organisation if they request additional time to confirm, until they notify you that the considerations have been satisfactorily completed..
- You may include NHS organisations in this study in advance of the deadline above where the organisation confirms by email to the CI and sponsor that the research may proceed.
- The document "[Collaborative working between sponsors and NHS organisations in England for HRA Approval studies, where no formal confirmation of capacity and capability is expected](#)" provides further information for the sponsor and NHS organisations on working with NHS organisations in England where no formal confirmation of capacity and capability is expected, and the processes involved in adding new organisations. Further study specific details are provided the *Participating NHS Organisations and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections of this Appendix.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A local collaborator will enable the provision of information about the study to potential participants at the participating NHS organisation.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

Study activities will be taking place under responsibility of university student and their academic supervisors outside the NHS. No requirements for access arrangements to NHS care facilities are anticipated.

GCP training is not a generic training expectation, in line with the [HRA statement on training expectations](#).

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Appendix I; Confirmation of R&D approval at hospital site (Chapter 8)

RE: Local study ID: 2017087. Confirmation of Capacity and Capability for non-portfolio research at [REDACTED]

AE [REDACTED]

To Franklin, John; Batterham, Alan; Atkinson, Greg
Cc researchdevelopment [REDACTED]

Fri 27/10/2017 08:27

You replied to this message on 27/10/2017 10:14.

statement-activities-CFS quals study.docx

93 KB

Dear Team,

RE: Local study ID: 2017087. Confirmation of Capacity and Capability for non-portfolio research at [REDACTED]
Full Study Title: A phenomenological study of experiences of physical activity in patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis.

This email confirms that [REDACTED] has the capacity and capability to deliver the above referenced study.

Please find attached our agreed Statement of Activities as confirmation.

[REDACTED]

Project Officer Assistant
Research & Development

[REDACTED]



Research study for patients with CFS/ ME

Participants are needed to take part in a study exploring the experiences of physical activity and exercise in patients with Chronic Fatigue Syndrome (CFS)/ Myalgic Encephalomyelitis (ME).

What is the study for?

We want to know more about CFS patients' experiences of exercise and physical activity from their point of view. There is some research on the use of exercise in the treatment of CFS/ ME however there is limited research exploring how people with this condition think/feel about physical activity and exercise.

What will be required?

If you are interested in taking part in this study please read the participant information sheet (PIS). If you decide to take part you would then participate in a one- off interview lasting between 45 and 60 minutes at Teesside University or at your own home. In this session, you will be asked a number of questions about your own experiences of physical activity, exercise and CFS/ ME.

What data will be collected?

We will collect information on your age, sex and the number of years that you have been ill with CFS. The rest of the data will be information about your experiences. No identifiable information will be shared with anybody outside the research team.

If you have any questions about this study or would like to participate, please contact

John Franklin

Senior Lecturer in Research Methods

School of Health and Social Care

Teesside University

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Email: j.franklin@tees.ac.uk

Telephone: 01642 (73) 8508



A phenomenological study of the experiences of physical activity in patients with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME).

Participant information sheet

Primary researcher: John Franklin, Teesside University

Research team: Professor Alan Batterham, Teesside University

Professor Greg Atkinson, Teesside University

Dr Samantha Harrison, Teesside University

We would like to invite you to take part in this research study however before you decide please read the following information. Please discuss any aspects of this study with anyone that you wish and please contact the research team and ask any questions that you may have.

What is the purpose of the study?

There have been a number of research studies assessing the use of exercise and physical activity in the management/ treatment of CFS/ ME however there is very little research exploring the experiences of physical activity from the perspective of CFS/ ME patients themselves. The aim of this study is try and understand from patients how they experience activity and how they believe this is linked to their illness. The study is also in part fulfilment of John Franklin's PhD in Health at Teesside University.

Why am I being invited to take part?

As a patient with CFS / ME you have been asked to participate as you are the patient group whose experiences we would like to explore. The inclusion criteria for this study are that participants must be adults over the age of 18 and have a diagnosis of CFS/ ME.

What is involved in this study?

This study will involve a one off interview lasting between 45minutes and 60 minutes. In this interview you will be asked to discuss your experiences of physical activity and exercise. This is not a test and there are no right or wrong answers, the study is designed to try and understand your experiences from your point of view.

Do I have to take part?

No. You do not need to take part. Participation in this study is completely voluntary and you should only participate if you feel happy with what is involved with the study and that you are happy for information about your experiences to be disseminated. Any information that is collected will be completely anonymised and no identifiable data will be shared with anybody outside of the study. As this study is anonymous taking part in this study will not inform any ongoing treatment or care.

What will happen if I do take part?

If you take part in this study you will be asked to participate in an interview either at Teesside University or at your own home. If the interview is conducted at Teesside University then this will be in a private room. The interviews will be conducted by John Franklin. Before the interview begins the study will be explained to you and you will be offered to opportunity to ask any questions. If you are happy to participate in the study you will be asked to provide informed consent. Following this the interview will take place. This will involve the researcher asking 5-6 questions to try and guide the interview on the topic of exercise and physical activity. You can terminate the interview at any point and you have the right to withdraw from the study up until 31st January 2018. This date has been set as we will begin to analyse your interview after this period you can no longer withdraw your data after this point. Once the data from all the interviews has been analysed the study will be written up and submitted to a peer reviewed journal for publication. Your GP will be notified of your involvement in the study with your consent but no identifiable data will be shared with your GP unless confidentiality has to be breached as a result of a disclosure. In the event that something is raised in your interview and confidentiality may need to be breached this will be fully discussed with the research team first before being shared with your GP. In the event that confidentiality has to be breached as a result of a disclosure this will be discussed with you fully beforehand.

What are the possible advantages and disadvantages and benefits of taking part?

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

There are no direct benefits for you as an individual for taking part in this study however we will use your data to try and provide a better understanding of your experiences from your point of view. There should be no disadvantages of taking part in this study; however, due to the nature of your illness you may become tired during the interview process and breaks can be taken at any time during the interview. If there are any questions that are raised which you don't want to discuss then you don't have to. If any topics/ questions are upsetting the interview can be paused or terminated and if you decide that after the interview you don't want your data to be analysed you can withdraw up to 31st January 2018.

Expenses and payments?

There are no payments or expenses available for taking part in this study.

What will happen to the information that is collected about me?

Your interview will be audiotaped and then transcribed. Once your interview has been transcribed, for the purpose of analysis and the write up of the study you will be referred to using a pseudonym such as participant 1, 2, etc. There will be 8 interviews including your own conducted and once all interviews have taken place they will be analysed for any themes (these are importance points that you raised in your interview). The research team will look for repeated themes across the interviews. As part of this process the three other academics named at the start of this document will assist in the analysis. This is to maintain the objectivity during the analysis of the data. Following the analysis process the findings will be discussed with a CFS/ ME Patient Advisory Group at Teesside University. This is called Public Patient Involvement (PPI) and it is a way of gaining a deeper insight into our interpretations and to try and ensure we have maintained our objectivity and our findings are a true reflection of your experiences. After this process the data will then be written in an academic research paper and published in peer reviewed journal. The study will also be a component of John Franklin's PhD thesis. Any identifiable data that will be collected as part of this study will be kept in a locked filing cabinet or on a password protected university server. After 1st June 2018, all identifiable data will be destroyed. No identifiable data will be shared with anybody outside of the research team and only non-identifiable data will be used in the data analysis and write up of this study. During the interview process if confidentiality has to be breached as a result of a disclosure, this will be discussed with the research team first and if deemed appropriate your GP may be contacted.

Withdrawing from the study

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

You have the right to withdraw at any point during the study; however, you cannot withdraw after 31st January 2018 as the data analysis process will have started. If you would like to withdraw your data up until this date you would simply email or telephone the primary researcher.

Who has approved the study?

This research study has been approved by Teesside University School of Health and Social Care Ethics board. West of Scotland Research Ethics Committee 3 and South Tees Hospitals NHS Foundation Trust R&D department.

What if something goes wrong?

If anything goes wrong, firstly please do accept my apologies for this, and if you want to complain then please contact: The Patient Advice and Liaison Service (PALS), email: stees.pals@nhs.net; tel: 0800 0282451, or on 01642 854807 / 01642 282657; Address: Patient Advice and Liaison Service, The James Cook University Hospital, Marton Road, Middlesbrough, TS4 3BW. If you would like to talk to someone at Teesside University, who knows about, but is not involved with this project, then please contact: Dr Alasdair MacSween the Chair of Teesside University School of Health and Social Care Research Ethics Committee. Dr Alasdair MacSween, Principle Lecturer in Research Governance; email: a.macsween@tees.ac.uk; tel: 01642 34 2965.

Who can I contact for more information/ who do I contact if I want to take part?

If you would like more information or you would like to participate in this study, please contact;

John Franklin

Senior Lecturer in Research Methods

School of Health and Social Care

Teesside University

Email: j.franklin@tees.ac.uk

Tel: 01642 (73) 8508

Director of Studies

Professor Alan Batterham

Investigating the Relationship Between Physical Activity/ Exercise and
CFS/ME

Professor in Exercise Science

School of Health and Social Care

Teesside University

Email: a.batterham@tees.ac.uk

Tel: 01642 (82) 7771

For independent advice about this study or if you have any concerns about this study please contact: Dr Alasdair MacSween, Principle Lecturer in Research Governance; email: a.macsween@tees.ac.uk; tel: 01642 34 2965.

This study is part of John Franklin's PhD. No Funding has been received for this study. No member of the research team has any conflict of interests to declare in relation to this study.



A phenomenological study of experiences of physical activity in patients with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME).

Informed Consent Form

Primary researcher: John Franklin

Please put your initials in the boxes to indicate your agreement with the corresponding statements.

1. I have read and understood the Participant Information Sheet (Version 3; 17/10/2017) for the above study and have had the opportunity to ask questions.

2. I meet the inclusion criteria for participation in the study.

3. I know that I have the right to withdraw at any time up to 31st January 2018

without giving reasons and without any of my rights being affected

4. I understand and agree that the interview will be audio recorded.

5. I understand that anonymised quotes will be used from the audio

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

recording and that my data will be kept confidential and stored for up to 10 years after which it will be confidentially destroyed.

6. I understand that if I decide to withdraw from the study I will be contacted to give consent before the data from my interview is shared with the patient advisory group

☐

7. I understand that my data will not have my name or anything identifiable in it, but will be linked to me by a participant number which will be stored separately from the data until 1st June 2018. After this date, all identifiable data will be destroyed.

☐

8. I agree that the research team will have access to the data and information collected about me.

☐

9. I agree for my GP to be contacted and informed of my involvement in this study

☐

A phenomenological study of experiences of physical activity in patients with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME).

Informed Consent Form

10. I agree to take part in this study.

☐

Name of Participant

Date

Signature

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Name of Researcher

Date

Signature

GP contact Detail

Please could you provide your GP information below;

GP name:

GP address

.....
.....
.....
.....

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Appendix; M; Interview Schedule (Chapter 8)

Q1 Hi, [name] please can you describe your illness (how long have been ill/ diagnosed) – How do you feel about physical activity/ exercise for people with CFS?

Q2. Please tell me about your experiences of physical activity/ exercise before you became ill? (hobbies/ fitness)

Q3 Please tell me about your experiences of physical activity/ exercise after you became ill - [explore whether different experiences were perceived as beneficial or harmful and what characterised them as such]

Q4 How do you think CFS affect different types of physical activity – [explore whether different experiences were perceived as beneficial or harmful and what characterised them as such]

Q5 How do you believe friends/ family think about you participating in physical activity/ exercise since you have become ill?

Do they help? How do they help? How does this make you feel?

*How do you explain to your friends and family to help them understand?
Does this work?*

Do they worry? Are they encouraging?

Topics to cover if these aren't discussed in the interview around structured exercise

- 1. Have you tried a structured exercise programme – why/ why not.
What type of exercise – was this beneficial/ harmful – why. How do you perceive this?*
- 2. Would you consider structured exercise [again] – what would impact on your decision to participate/ try an exercise or physical activity programme?*

Is there anything else that you would like to add?

H2.23 Centuria Building
Teesside University
Middlesbrough
TS1 3BA

Telephone: 01642 273 408

Email: j.franklin@tees.ac.uk

[Insert GP address]

[Insert date]

[Insert patient name] participation in study: A phenomenological study of
experiences of physical activity in patients with Chronic Fatigue Syndrome /
Myalgic Encephalomyelitis.

Dear Dr [Insert GP name]

I am writing to inform you that [insert patient name] has volunteered to be a
participant in the research study 'A phenomenological Study of Experiences
of physical activity in patients with Chronic Fatigue Syndrome / Myalgic
Encephalomyelitis.' I will be collecting, analysing and storing all data. No
action is required by yourself; however, if any incidental findings are made
during this study you may be contacted. If you would like any further
information about the study I would be happy to discuss this with you. For
independent advice about this study or if you have any concerns about this
study please contact: Dr Alasdair MacSween, Principle Lecturer in Research
Governance; email: a.macsween@tees.ac.uk; tel: 01642 34 2965.

Yours faithfully

John Franklin

Investigating the Relationship Between Physical Activity/ Exercise and
CFS/ME

Senior Lecturer in Research Methods

Teesside University

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

Appendix O; Patient Advisory Group Advert



Teesside
University

**Teesside University CFS/ ME Patient
Advisory Group**

I am a senior lecturer and PhD students at Teesside University and I am undertaking research assessing physical activity and exercise and CFS/ ME. To help with this I would like to develop an advisory group. The aim of this would be to discuss the development of research and to discuss findings from research. My main aim is to ensure that research is done with you as a patient group and not done 'to' you.

This is NOT an invitation to take part in the research study however your involvement is an important part of the research process.

If you choose to be involved you may be asked to:

1. Look over results of research and give your opinion
2. Provide information and discussion around possible exercise and physical activity interventions.
3. To be involved in the development of research studies into understanding CFS/ ME.

This may involve coming to Teesside University for an hour to discuss research and/ or may involve some discussion over email about research and research findings.

Thank you in advance for taking the time to read this letter and for considering being involved in such an important part of this research project.

If you are interested in finding out more, please contact

John Franklin

Senior Lecturer in Research Methods

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Information for Patient Advisory Group

Qualitative study

Overview

For this study I have interviewed 6 people who have a diagnosis of CFS/ME. The aim of these interviews was to try and understand how people with CFS/ME experience and perceive their illness, specifically in relation to physical activity and exercise. The 6 interviews all lasted around 1 hour, plus or minus about 15 minutes. Following the interviews, I transcribed these, word for word and then read over these to try and identify patterns in the interviews which may help paint a picture of their experiences. The specific method used in this study is called interpretive phenomenological analysis (IPA).

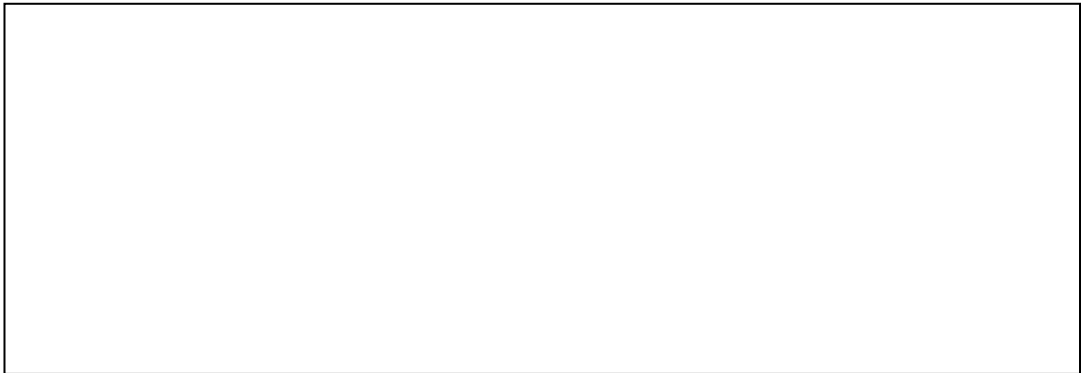
Below are four themes that we have developed (a theme is the name given to the related patterns that we believe are present in the experiences). What I would like is for you to look over these and see if you can recognise your experience in these. I have made some broad questions which may help with this or guide you however please don't think you have to use these. There are four themes with supportive quotes, however, please again don't think you have to look over all four. I appreciate any feedback you can provide. If you want to talk about these in more detail, please let me know.

One final point, is in research of this nature we name the themes and codes, so if you think we've made a good point but called it the wrong name, this also is really important and any suggestions you have I would greatly appreciate.

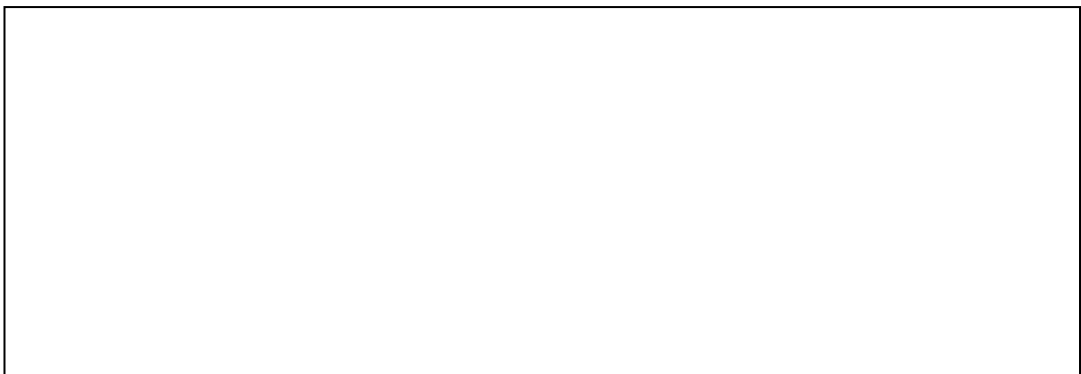
Questions you might want to consider

1. Do any of the themes below reflect any of your experiences? Please add any comments you think might be helpful.

2. Do you think that any of the themes are not quite right?



3. Do you think there's anything in particular that we've captured well?



4. Do you think we've misunderstood anything?



Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

5. Do have any overall comments or anything you'd like to add

[illegible]

Findings

From the data we have identified four master themes that we think are important, I've also listed some of the contributing themes which we think are related to each master theme. I have then provided a quote or quotes with each theme below.

Master theme	Coming to terms with being ill	Losing sense of self	Hiding symptoms but seeking compassion	Small wins and flexible approach
Emerging/ contributing themes	Reaching crisis point before seeking help Trying to hit it head on Exhaustion	Fundamental change Loss of role/ family role Lack of socialising/ engaging in societal activities	Hidden illness Feelings of lack of legitimacy Fear of negative evaluation	Wanting to do more Fear symptoms might worsen Consequences of doing too much

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

	Getting worse even though I've slowed down	Isolation Forgetfulness Loss of confidence Activity and mood	Wanting people to understand Wanting empathy	Mini independence Unpredictability Requires a flexible approach It still catches me out
--	--------------------------------------------	-----------------------------------------------------------------------------------	-----------------------------------------------------	--------------------------------------------------------------------------------------------------------------

Below is an edited and condensed version for ease and accessibility, please let me know if you would like to see the more in-depth version.

5. Coming to terms with being ill

This theme relates to the descriptions of initial illness. Participants described trying to beat their illness and trying to hit it head on that resulted in a worsening of symptoms. This was then described alongside exhaustion and participants described the initial period of illness where they had slowed down, yet the illness continued to worsen. In particular this theme relates to how it was perceived that the illness could be '*beaten*'.

1.1 Reaching crisis point

'I was trying to get back to normal and, the tiredness and the pain just got worse. In fact, it got to a point where I couldn't really move off the settee, I was in that much pain. I then started going to the GP...' P1. Participants often described this delay as they thought they were 'just getting old' and they thought it was just 'one of those things'.

1.2 Exhaustion

'I thought, oh, I can fight my way through this, if I battle on, if I push myself really hard, what will happen is I'll sort of, crack it and I'll be fine' P1. Notably language and metaphors around '*battling*' and conflict.

'I was like, I won't be beaten, I'm just going to push myself, I'm going to do it, and I made myself so ill, I ended up in bed for days, I couldn't physically move and it terrified me' P2.

'Initially it was overwhelming, the fatigue, to the point that, at its worst, I couldn't, the energy required to get out of bed' P6. This was echoed by participant 3 who described this as an episode of extreme exhaustion. *'I remember it being very, very hard, was, when you're feeling so tired, all you want to do is lie down and you don't want to engage and you just want to sleep... it was so much more than any level of normal tiredness... it was a totally different extreme' P3.*

1.3 Continued to get worse even after slowing down

Participants described a period when they became ill when they had made initial modifications to their lifestyle however their symptoms continued to deteriorate, *'once I finished work... you think you'd get better, you know by not putting that extra pressure on, but it seemed to get worse, as in more, more fatigue...' P5.*

Optional space for notes

6. Losing sense of self

2.1 Fundamental change

This theme relates to how participants described themselves since becoming ill and made comparisons to how they perceived themselves prior to becoming ill. Participants spoke about how the illness had fundamentally changed them, *'I kept thinking, I was becoming a person that I didn't recognise and I think it fundamentally, looking back, it must have just been because I was so tired, I just didn't trust my thoughts or didn't trust my, I don't know, just didn't trust in myself anymore,' P6*

'Probably sounds a little bizarre but you were almost removed from your own being... I was almost following myself as in I was, my consciousness was almost removed from my physical self... a feeling of being totally detached... I felt like I was just going through the motions... it was a general feeling of detachment' P3.

2.2 Loss of role

In relation to tiredness prior to illness, *'you've almost got to the point where you've earned the right to feel a bit tired because you've had a really productive day, you've had a really busy day and you've achieved a lot and you know, you get to that point where you think, blimey that was a good day, I now need to get a good night sleep.'* P3

'I say active because obviously... we used to, be very active, go on a lot of walks and things like that, Roseberry Topping, is a good example. We'd go up there take the dog. Lots of woodland walks, that kind of thing.' P1

'But I couldn't stand anything that was touching me, in fact the reason I ended up growing a beard is because I couldn't I have a razor near my face, it's sort of everything set me off, it was that sensitive to it'.

'They say that I look, I look tired and they say that I, they say I change colour, that I drain colour and things like that, and they say that I fade away. They say it's like a light's on but nobody's at home' P6.

2.3 Isolating

'I would like to get to a point where I do have more energy to do fun stuff but I guess that's just part of it, isn't it, that the fun stuff goes, that's the first thing to go, is anything fun,' P4.

'It was also affecting friendships, where normally people would actually contact me and say, you know, do you fancy doing something at the weekend or do you fancy doing this evening after work, and I had absolutely no energy to do it'.

2.5 Forgetfulness

'I had to sit down because I was too tired, I couldn't kind of keep up with the conversation because I'm, I'm forgetful, I can't remember the most simple of words' P2.

2.6 Mood and activity

'Yes, I'm really pleased that happened and you sort of get that feeling of elation and as a result, my energy levels would go up, but just for a short period of time, and then they would dip again' P3.

Optional space for notes

7. Hiding symptoms but seeking compassion

This theme relates to how participants would describe feeling ill, while also being aware that from the point of view of others, they may appear fine. This theme relates to the idea of the illness being hidden and how this can produce a feeling of lack legitimacy around the illness and a fear of negative evaluation by others. This results in a desire for empathy and understanding.

3.1 Hidden illness

'I guess what I'm trying to share is that if I'd had some illness that was, you know, easily recognisable, easily diagnosable, treatable, I wouldn't have had an issue with that... because it's this ambiguous illness... got this huge question mark about it from some people' P6

'She doesn't realise how bad I am until something like I can't get up from the table or something like that... you see at work they just see me getting on with it and they don't sort of see, it's the bit at home' P4.

'They don't realise how, when I take my make-up off and stuff, that I feel really ill' P2.

3.2 Feeling a lack of legitimacy

We noted emotionally charged language used to describe the illness which we again attribute to wanting to emphasise the seriousness of the condition linked to feelings of wanting legitimacy, *'crippling's of chest pains'* and *'almost like something was gnawing away at it' P1*. This was accompanied by use of imagery and metaphors to bolster the understanding of their symptoms, again we attribute this to a feeling of wanting legitimacy and to convey the seriousness of their illness.

Of note that for those who didn't have metaphors to aid with their description, found it difficult to articulate their symptoms, *'for me it's like a weakness... it's almost like you're not sure if your body will carry you across the room... it's hard to describe actually, hard to articulate' P6.*

7.5 Fear of negative evaluation

This relates to discussions around how they believed others may perceive them.

'Well you don't want to show weakness... I think other people hear it and that look comes over, that look of shock and then pity' P4.

'I'm just going to have a walk in this bit of the garden and you know, so you can build it up and it feels quite safe and like, nobody's there, nobody's like watching you... it might sound crazy because I probably look really well and I think, I don't think I can make my legs move and it's horrible, horrible thing. But I think somebody might be looking at me and think, what's wrong with that women' P6.

'During the conversation I thought, I've, do you, I feel so ill, I feel terrible... so while I was chatting with my friend I've got this inner monologue going on in my head saying... you're alright, you're not dying... and at the same time trying to chat and act as if everything is ok' P2.

3.4 Wanting understanding and compassion

'Their natural instinct is that they don't want you to do anything, they just want you to rest all the time... one of the hardest things now is getting them to actually let me do some stuff... because I can't live my life not doing things because it might have a negative impact'.

'As long as they listen, so if I say, look I appreciate you wanting me to do this but I've got to go home and function at home as well...if I thought they weren't listening to what I was saying and not taking me seriously then I probably wouldn't go back' P2.

Optional space for notes

8. Small wins and flexible approach

This theme is related to descriptions relating to how participants had modified their lifestyles to manage the illness. Participants talked about strategies they had tried and tested to maintain a degree of independence however the illness still caught them out at times. They all described the importance of small incremental '*wins*' however the illness was always there and could still '*catch them out*'.

4.1 Wanting to do more

'I don't want to go to bed and lie down and go to sleep because I'm still going to feel, I don't know, I know I'll still feel the same, so I still want to be present if that makes sense' P6.

4.2 Fear symptoms might worsen

'it terrifies me, to, get to a point where I'm not doing anything, I don't want to be that person, I want to go out and have a walk, it's not a big thing, but it's a big thing to me' P2.

4.2 Consequences of doing too much

'I'd been absolutely fine, I'd been walking, my legs weren't even aching and then it literally was, like no energy and it was the hardest thing ever just to do that five minutes back to the hotel' P4 and 'I ended up in bed for days and I couldn't, I physically couldn't move and I, and I, it terrified me' P2.

'If you imagine, like when you were a teenager and you were drunk but pretending to your parents that you weren't drunk, that's how I feel having a conversation with someone, I feel like I'm thinking about every single word and trying to hide it almost' and 'it was so weird, like I'd been drugged almost' P4.

4.3 Small wins and mini independence

Participants spoke of tasks that they viewed as their personal jobs that they liked to complete, '*you know I still try to maintain this kind of level of minute independence*' P1. These tasks were also viewed as a measure of how ill they were feeling, '*you know, and do you know what's really stupid, for me, god, a big achievement is getting in the shower and putting my makeup on. And I think, do you know what, I've done that today, that is great*' P2.

'I'll just look out the window, I didn't day have a rest, I'm just going to look out the window, because I felt having a rest didn't feel very positive... that felt to me like a success, rather than, oh I'll have a rest, felt like failure... it as only recently and I thought I didn't look out the window... that was like amazing, that's marvellous, that's fantastic' P6.

'just going from that point of not feeling useless... more a case of, it is what it is and almost acceptance of it... it impact on the level of mood and you know, I think that feeling of despair and depression wasn't quite as great... just feeling like by doing an awful lot less, you're still doing something' P3.

4.4 unpredictability and need for flexibility

Alongside this, participants described the unpredictability of the illness and even after planning for events where they were aware that they could be overexerting themselves their symptoms could still worsen.

'It was almost a fear of setting a target that I wasn't going to achieve, that was going to knock me back, impact on me negatively'. This concern over not achieving a goal and the negative impact this may have was also described by participant 6 'maybe I also got to the point of the fatigue getting really bad by putting a lot of pressure on myself... I'm worried if I put too much pressure on myself that I just, you know, go again'.

Participant 5 described the process he goes through when deciding how much activity to participate in, *'so it's up and down, there's no set two or three days, I can't say if I do this today I'll be alright tomorrow or I'll work at this thing, it's pretty much wake up in the morning and say right, what do I feel like...'*

'Sometimes I can surprise myself... I mean I'm not stupid and I do it and I know, well I'm gonna pay for that because I didn't feel great doing it. But sometimes my symptoms are not horrendous, and I can push myself that little bit further, I don't know why that is' P2.

4.5 It still catches me out

'I'll suddenly be stood there, and I can't find a word... or I find that I've been starring at the computer screen and like ten minutes has gone and I've not done anything' P4.

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

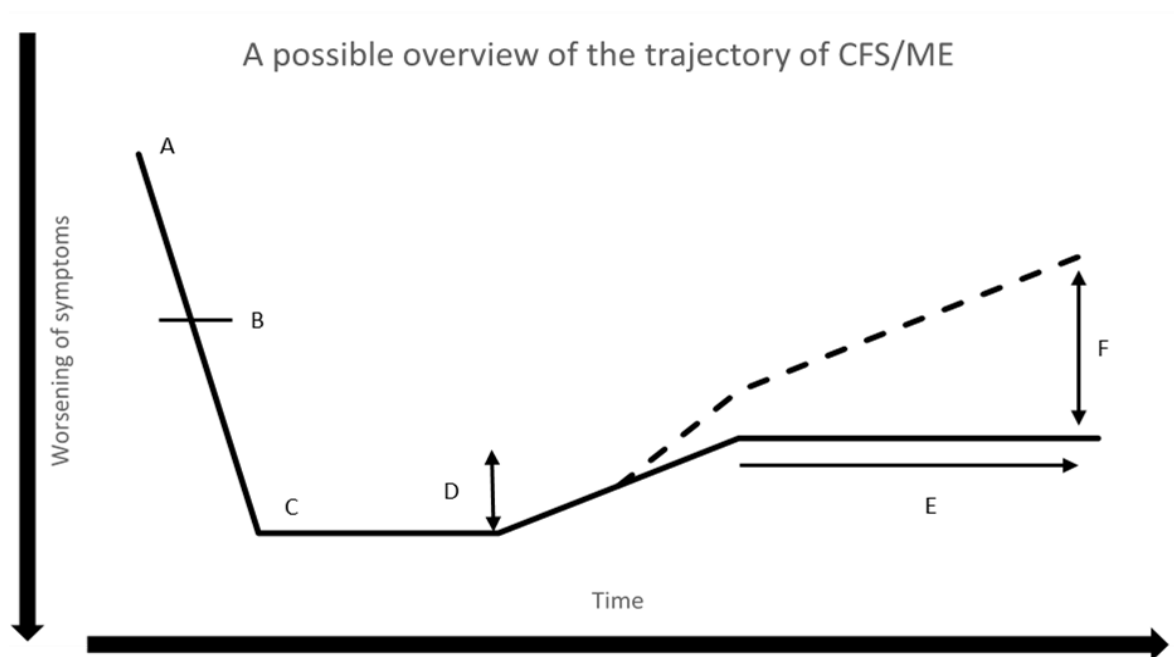
Following exercise P5 described the illness sneaking, catching him unawares, *'I'm hoping it's not this coming, this sneaking in and coming again'* P5.

Optional space for notes

Information to Patient Advisory Group

Possible model of illness

Below is a diagram that I have created based on the discussions with people with CFS/ME. I have used this information to try and develop a possible course of the illness. I am interested to see if you think this is a fair reflection of your experience of CFS/ME. Please note that although I have used a smooth line I understand the line should fluctuate; however, for ease of understanding, I have kept this smooth.



Key

A – Beginning of illness – unknown cause

Investigating the Relationship Between Physical Activity/ Exercise and CFS/ME

B – Symptoms continue to worsen – may have taken steps to manage illness such as taken time from work – symptoms continue to worsen

C – Symptoms reach worst point, followed by a period of severe illness

D – Initial remission – a marginal improvement in symptoms

E – Self-management – an equilibrium is found with some degree of functionality. Some achieve a minimal degree of activity, some are able to return to a relative degrees of pre-illness levels.

F – May achieve a degree of “remission” (or a new “normal”) within this range

How do you think this applies to your own experiences of CFS/ME?

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